Co.Nr	NMR-data
9-08	^{1}H NMR (300MHz, DMSO-d^6) δ 3.77 (s, 3H), 4.37 (d, J=5.8Hz, 2H), 5.12-5.19 (3H), 7.00 (d, J=8.9Hz, 2H), 7.35-7.43 (m, 4H), 7.44-7.52 (m, 2H), 7.72-7.76 (m, 1H), 8.07-8.10 (m, 1H).
9-10	^{1}H NMR (300MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.87 (s, 3H), 5.22 (s, 2H), 6.82 (d, J=2.3Hz, 1H), 6.95 (d, J=8.7Hz, 2H), 7.07-7.12 (m, 2H), 7.13-7.15 (m, 1H), 7.32 (d, J=9.0Hz, 2H), 7.47-7.55 (m, 1H).
9-12	^{1}H NMR (500MHz, $CDCl_3$) δ 2.08 (s, 3H), 3.83 (s, 3H), 5.16 (s, 2H), 6.53 (s, 1H), 6.91 (d, J=8.7Hz, 2H), 7.09 (s, 1H), 7.11 (d, J=8.7Hz, 2H), 7.28-7.37 (m, 5H).
9-13	^{1}H NMR (500MHz, $CDCl_3$) δ 2.09 (s, 3H), 5.14 (s, 2H), 6.51 (s, 1H), 7.10 (dd, J=9.8Hz, J=2.0Hz, 1H), 7.13 (dd, J=8.4Hz, J=2.5Hz, 1H), 7.23 (m, 3H), 7.39 (m, 3H), 7.48 (t, J=8.2Hz, 1H).
9-14	^{1}H NMR (500MHz, $CDCl_3$) δ 2.08 (s, 3H), 3.84 (s, 3H), 5.12 (s, 2H), 6.49 (s, 1H), 6.93 (d, J=8.8Hz, 2H), 7.13 (m, 4H), 7.19 (s, 1H), 7.48 (t, J=8.2Hz, 1H).
9-16	^{1}H NMR (300MHz, $CDCl_3$) δ 1.64 (s, 2H), 2.07 (s, 3H), 3.83 (s, 3H), 5.12 (s, 2H), 6.48 (s, 1H), 6.93 (d, J=9.0Hz, 2H), 7.13-7.28 (m, 5H), 7.40-7.46 (m, 1H).
9-17	^{1}H NMR (300MHz, $CDCl_3$) δ 2.65 (t, J=6.7Hz, 2H), 3.25 (s, 3H), 3.44 (t, J=6.7Hz, 2H), 3.82 (s, 3H), 5.09 (s, 2H), 6.58 (s, 1H), 6.90 (d, J=8.7Hz, 2H), 7.06 (s, 1H), 7.11 (d, J=8.7Hz, 2H), 7.23-7.32 (4H).
9-18	^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.82 (s, 3H), 5.11 (s, 2H), 5.99 (s, 1H), 6.88-6.95 (m, 2H), 7.08-7.15 (m, 2H), 7.20-7.30 (m, 3H), 7.40-7.50 (m, 1H).
10-28	^{1}H NMR (300 MHz, DMSO-d^6) δ 0.92 (d, J=5.6Hz, 6H), 1.48-1.63 (m, 3H), 3.90-4.02 (m, 2H), 6.72 (d, J=7.2Hz, 1H), 7.32 (d, J=8.4Hz, 1H), 7.96-8.04 (m, 2H), 8.08 (d, J=7.2Hz, 1H).
11-03	^{1}H NMR (500MHz, DMSO-d^6) δ 3.80 (s, 3H), 5.11 (s, 2H), 6.62 (dd, J=2.1Hz and 7.2Hz, 1H), 6.66 (d, J=2.0Hz, 1H), 7.02 (d, J=8.9Hz, 2H), 7.09-7.17 (m, 3H), 7.36-7.42 (m, 1H), 7.70 (dd, J=2.1Hz and 6.8Hz, 2H), 7.85 (d, J=7.1Hz, 1H).
12-06	^{1}H NMR (300 MHz, DMSO-d^6) δ 3.78 (s, 3H), 5.12 (s, 2H), 7.00 (d, J=9.0Hz 2H), 7.40-7.50 (m, 4H), 7.77 (d, J=9.0Hz, 2H), 8.14 (s, 1H), 8.39 (s, 1H).
13-01	^{1}H NMR (DMSO-d^6) δ 5.16 (s, 2H), 6.67 (d, J=7.2Hz, 1H), 7.14-7.18 (m, 2H), 7.37-7.39 (m, 2H), 7.51 (m, 1H), 7.60 (d, J=7.2 Hz,1H), 7.66 (m, 1H), 7.71 (m, 1H), 8.23 (m, 1H).
13-05	^{1}H NMR (300 MHz, DMSO-d^6) δ 0.96 (t, J=7.4Hz, 3H), 1.40-1.72 (br. s, 1H), 1.72-1.87 (m, 2H), 2.99 (t, J=7.2Hz, 2H), 3.47 (t, J=6.9Hz, 2H), 3.95 (t, J=7.4Hz, 2H), 6.35-6.47 (m, 1H), 6.79 (d, J=8.4Hz, 2H), 6.99-7.12 (m, 4H), 7.34-7.42 (m, 1H), 7.91-8.02 (m, 1H).
13-06	^{1}H NMR (300MHz, $CDCl_3$) δ 0.90 (t, J=7.7Hz, 3H), 1.74 (q, J=8.5Hz, 2H), 3.06 (t, J=6.6Hz, 2H), 3.73 (s, 3H), 3.89 (t, J=7.4Hz, 2H), 4.17 (t, J=6.6Hz, 2H), 6.75-6.83 (m, 3H), 6.98 (t, J=7.2Hz, 2H), 7.18 (d, J=8.2Hz, 2H), 7.29 (t, J=8.2Hz, 1H), 7.92 (d, J=8.2Hz, 1H).
14-01	^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J=7.4Hz, 3H), 1.55-1.70 (m, 2H), 2.75-2.90 (4H), 3.72 (s, 3H), 3.81 (t, J=7.3Hz, 2H), 6.60 (s, 1H), 6.75 (d, J=8.7Hz, 2H), 6.97 (d, J=8.6Hz, 2H), 7.40-7.50 (m, 1H), 7.62-7.68 (m, 2H), 8.40-8.45 (m, 1H).
15-04	^{1}H NMR (300MHz, $CDCl_3$) δ 5.52 (s, 2H), 6.80 (d, J=9.5Hz, 1H), 7.13-7.24 (4H), 7.25-7.30 (m, 2H), 7.40-7.48 (m, 1H), 7.58 (dd, J=1.5Hz and 7.9Hz, 1H), 7.75 (d, J=9.5Hz, 1H).
16-01	^{1}H NMR (500MHz, DMSO-d^6) δ 3.95 (d, J=5.9Hz, 2H), 5.03 (s, 2H), 5.97-6.02 (m, 1H), 6.40 (d, J=9.3Hz, 1H), 6.50-6.55 (m, 1H), 6.57 (d, J=7.7Hz, 2H), 7.01-7.06 (m, 2H), 7.28 (d, J=8.5Hz, 2H), 7.35-7.39 (m, 2H), 7.44 (dd, J=2.5Hz and 9.3Hz, 1H), 7.77 (d, J=2.1Hz, 1H).

Co.Nr	NMR-data
16-02	^{1}H NMR (500MHz, DMSO-d^6) δ 3.69 (s, 3H), 4.74 (s, 2H), 5.07 (s, 2H), 6.45 (d, J=9.3Hz, 1H), 6.82-6.87 (m, 2H), 6.88-6.93 (m, 2H), 7.29 (d, J=8.5Hz, 2H), 7.40 (d, J=8.5Hz, 2H), 7.52 (dd, J=2.5Hz and 9.0Hz, 1H), 7.93 (d, J=2.3Hz, 1H).
16-03	^{1}H NMR (500MHz, DMSO-d^6) δ 4.80 (s, 2H), 5.06 (s, 2H), 6.45 (d, J=9.3Hz, 1H), 6.91-6.96 (m, 1H), 6.96-6.99 (m, 2H), 7.12-7.17 (m, 1H), 7.25-7.30 (m, 2H), 7.36-7.43 (m, 2H), 7.53 (dd, J=2.5Hz and 9.3Hz, 1H), 7.99 (d, J=2.3Hz, 1H).
16-04	^{1}H NMR (500MHz, DMSO-d^6) δ 4.82 (s, 2H), 5.10 (s, 2H), 6.45 (d, J=9.4Hz, 1H), 6.91-6.96 (m, 1H), 6.97 (d, J=7.8Hz, 2H), 7.13-7.19 (m, 1H), 7.24-7.30 (3H), 7.45 (dd, J=2.3Hz and 10.1Hz, 1H), 7.55 (dd, J=2.3Hz and 9.3Hz, 1H), 7.90 (d, J=2.3Hz, 1H).
16-05	^{1}H NMR (300MHz, $CDCl_3$) δ 3.71 (s, 3H), 4.67 (s, 2H), 5.05 (s, 2H), 6.39-6.58 (m, 4H), 7.01-7.06 (m, 2H), 7.12 (t, J=8.2Hz, 1H), 7.19 (s, 1H), 7.32-7.38 (m, 2H).
16-06	^{1}H NMR (300MHz, $CDCl_3$) δ 1.91 (p, J=7.7Hz, 2H), 2.49 (t, J=7.4Hz, 2H), 3.85 (t, J=5.9Hz, 2H), 4.98 (s, 2H), 6.49 (d, J=9.2Hz, 1H), 6.78 (d, J=8.7Hz, 2H), 6.86-7.24 (m, 7H), 7.30 (t, J=8.4Hz, 1H).
16-08	^{1}H NMR (300MHz, $CDCl_3$) δ 0.89 (d, J=6.1Hz, 6H), 1.18-1.23 (m, 1H), 1.52-1.61 (m, 2H), 3.71 (s, 3H), 3.86 (t, J=7.9Hz, 2H), 4.65 (s, 2H), 6.52 (d, J=9.2Hz, 1H), 6.75-6.82 (m, 4H), 7.19-7.26 (m, 1H), 7.30 (dd, J=2.4Hz, J=9.2Hz, 1H).

PHARMACOLOGY

The compounds provided in the present invention are positive allosteric modulators of mGluR2. As such, these compounds do not appear to bind to the orthosteric glutamate recognition site, and do not activate the mGluR2 by themselves. Instead, the response of mGluR2 to a concentration of glutamate or mGluR2 agonist is increased when compounds of Formula (I) are present. Compounds of Formula (I) are expected to have their effect at mGluR2 by virtue of their ability to enhance the function of the receptor. The behavior of positive allosteric modulators, more particular the ones described by Formula (I), at mGluR2 is shown in Example A, which is suitable for the identification of such compounds.

EXAMPLE A

[^{35}S]GTPγS binding assay

The [^{35}S]GTPγS binding is a functional membrane-based assay used to study G-protein coupled receptor (GPCR) function. This method is using a binding assay to assess the initial step in receptor-mediated G protein activation in membranes prepared from cells expressing recombinant GPCR or using membranes from discrete area of the rat brain. In brief, the assay is measuring the activation of G proteins by catalyzing the exchange of guanosine 5'-diphosphate (GDP) by guanosine 5'-triphosphate (GTP) at the α subunit. The GTP-bounded G proteins dissociate into two subunits, Gα–GTP and Gβγ, which in turn regulate intracellular enzymes and ion channels. GTP is rapidly hydrolysed by the Gα-subunit (GTPases) and the G protein is deactivated and ready for new GTP exchange cycle (Harper (1998) Curr Protoc Pharmacol 2.6.1-10, John Wiley & Sons, Inc.). [^{35}S]GTPγS, a non-hydrolyzed analogue of GTP, is used for this purpose.

This method is widely used to study receptor activation of G protein in membranes prepared from rat brain tissue, including mGluR2 receptors (Schaffhauser et al 2003, Pinkerton et al, 2004). mGluR2 receptors are expressed in the rat brain cortex (Mutel et al (1998) J. Neurochem. 71:2558-64; Schaffhauser et al (1998) Mol. Pharmacol. 53:228-33) and are coupled to Gαi-protein, a preferential coupling for this method. The

study of the pharmacological characterisation of metabotropic glutamate receptor-mediated high-affinity GTPase activity (Nishi et al (2000) Br. J. Pharmacol. 130:1664-1670) showed that the activation of G-proteins in rat cerebral cortical membranes is mediated by group II mGluRs, and in particular by mGluR2.

[^{35}S]GTPγS binding assay using cortical rat brain membranes preparation was used and adapted from Schaffhauser et al ((2003) Mol. Pharmacol. 4:798-810) for the detection of the positive allosteric modulator properties of the compounds of this invention on native rat mGluR2. In order to eliminate the possible interference with group III Gαi-protein coupled mGluRs (mGluR4, mGluR7, mGluR8; mGluR6 is not expressed in the cortex (Laurie et al (1997) Neuropharmacol. 36:145-52)), the potentiation of the response to a selective mGluR2 agonist, such as DCG-IV (Cartmell et al. (1998) Br. J. Pharmacol. 123(3):497-504) or LY379268 (Monn et al. (1999) J. Med. Chem 42:1027-40), by compounds described in the present invention was performed.

Membrane preparation. Cortices were dissected out from brains of 200-300 g Sprague-Dawley rats (Charles River Laboratories, L'Arbresle, France). Tissues were homogenized in 6 volumes (vol/wt) of 10% sucrose at 4°C using a glass-teflon homogenizer. The homogenate was centrifuged at 1250g for 10 min, and the supernatant was centrifuged at 40,000g for 20 min (4°C). The pellet was resuspended in 25 ml water using a Polytron disrupter (Kinematica AG, Luzern, Switzerland) and centrifuged for 10 min at 3000 g. (4°C). The supernatant was centrifuged at 40,000g for 20 min (4°C). The supernatant was discarded and the pellet washed twice by resuspension in 10 volumes 5 mM HEPES-KOH, pH 7.4. The homogenate was frozen and thawed twice and centrifuged at 40,000g for 20 min. The final pellet was resuspended in 5 mM HEPES-KOH, pH 7.4 and stored at -80°C before its use. Protein concentration was determined by the Bradford method (Bio-Rad protein assay, Reinach, Switzerland) with bovine serum albumin as standard.

[^{35}S]GTPγS binding assay. Measurement of mGluR2 positive allosteric modulators properties in rat cortical membranes was performed as follows: rat cortical membrane (1.5 μg) were incubated in 96-well microplates for 15 min at 30°C in assay buffer (50 mM HEPES pH 7.4, 100 mM NaCl, 5 mM $MgCl_2$, 10 μM GDP, 10 μg/ml saponin, EGTA 0.2 mM) with increasing concentrations of positive allosteric modulator (from 1

nM to 10 μM) and a minimal concentration of DCG-IV or LY379268, a selective mGluR2 agonist, that has been determined in previous experiments and that corresponds to the EC_{20}, a concentration that gives 20 % of the maximal response of the agonist, and is in accordance to published data (Pin et al. (1999) Eur. J. Pharmacol. 375:277-294). Likewise, 10-point concentration-response curves of an mGluR2 selective agonist such as DCG-IV or LY379268, were tested in the absence or in the presence of 3 or 10 μM of positive allosteric modulator in order to detect a leftward-shift of the concentration-response curve of the agonist (appreciated by a decrease in the EC_{50}) and/or an increase of its maximal efficacy. After addition of 0.1 nM [^{35}S]GTPγS to achieve a total reaction volume of 200 μl, microplates were shaken for 1 min and further incubated at 30°C for 30 min. The incubation was stopped by rapid vacuum filtration over glass-fiber filter plates (Unifilter 96-well GF/C filter plates, Perkin-Elmer, Schwerzenbach, Switzerland) microplate using a 96-well plate cell harvester (Filtermate, Perkin-Elmer, Downers Grove, USA). The Unifilter plate was washed three times with 300 μl of ice-cold wash buffer (20 mM HEPES pH 7.4, 100 mM NaCl). When filters are dried, 40 μl of liquid scintillation cocktail (Microscint 20) was added to each well. The amount of membrane-bound [^{35}S]GTPγS is measured using a 96-well plate reader (Top-Count, Perkin-Elmer, Downers Grove, USA). Non specific [^{35}S]GTPγS binding is determined in the presence of 10 μM of GTP.

Data analysis. The concentration-response curves of representative compounds of the present invention in the presence of EC_{20} of mGluR2 agonist were generated using the Prism Graph-Pad program (Graph Pad Software Inc, San Diego, USA). The curves were fitted to a four-parameter logistic equation (Y=Bottom + (Top-Bottom)/(1+10^((LogEC$_{50}$-X)*Hill Slope) allowing determination of EC_{50} values. Each curve was performed using triplicate sample per data point and 10 concentrations. The concentration-response curves of a selective mGluR2 agonist in the absence or in the presence of representative compounds of the present invention were also generated using Prism Graph-Pad program (Graph Pad Software Inc, San Diego, USA). The curves were fitted to a four-parameter logistic equation (Y=Bottom + (Top-Bottom)/(1+10^((LogEC$_{50}$-X)*Hill Slope) allowing determination of EC_{50} values of the selective mGluR2 agonist. Each curve was performed using triplicate sample per data point and 10 concentrations.

Data presented in the Figure C below represent the ability of 10 μM of Compound 4-16 to increase the [GTPγ^{35}S] binding induced by 50 nM of DCG-IV, an mGluR2 agonist. Said compound has no statistically significant agonistic activity when tested in the absence of 50 nM DCG-IV, as compared to buffer value (0% of maximal response). Instead, when compounds are added together with an mGluR2 agonist like glutamate or DCG-IV, the effect measured is significantly potentiated compared to the effect of the agonist alone at the same concentration. Each bar graph is the mean and S.E.M. of triplicate data points and is representative of three independent experiments.

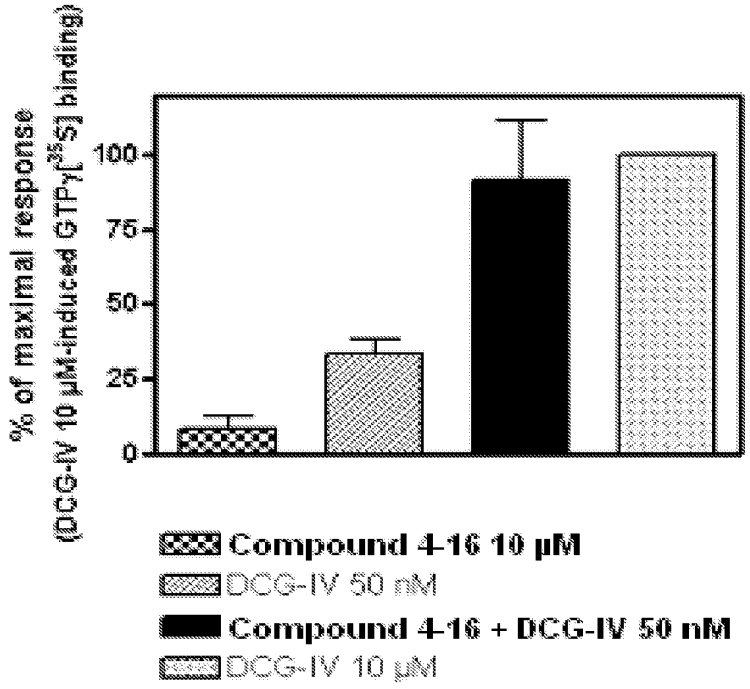


Figure C

Table 19 shows representative compounds of the present invention that were clustered into three classes according to their ability to leftward-shift the concentration-response curve of a selective mGluR2 agonist such as LY379268 and/or to increase its maximal efficacy.

Table 19 : Activity data for selected compounds

Compound no.	Activity
15-04	+
7-02	+
11-03	+
9-18	+
12-06	+
7-14	+
15-02	+
9-17	+
13-01	++
2-32	++
2-55	++
3-02	++
6-16	++
6-73	++
3-17	++
2-61	++
16-07	++
9-04	++
4-20	+++
4-47	+++
6-65	+++
9-06	+++
5-13	+++
10-28	+++
13-04	+++
13-05	+++
10-30	+++

(+) : left-ward shift of agonist mGluR2 concentration-response curve [< 2]
(++) : left-ward shift of agonist mGluR2 concentration-response curve [2- to 3.5-fold]
(+++) : left-ward shift of agonist mGluR2 concentration-response curve [> 3.5]

Thus, the positive allosteric modulators provided in the present invention are expected to increase the effectiveness of glutamate or mGluR2 agonists at mGluR2, and therefore, these positive allosteric modulators are expected to be useful for treatment of various neurological and psychiatric disorders associated with glutamate dysfunction described to be treated herein and others that can be treated by such positive allosteric modulators.

EXAMPLE B

Animal Models of Schizophrenia

Phencyclidine (PCP) model of schizophrenia PCP-induced increases in locomotor ambulation are a widely accepted animal model of schizophrenia. This model is based on the evidence that phencyclidine induces a schizophrenia-like syndrome in humans including increased motor behaviors, disruption of cognition and impairment of working memory (Steinpreis RE (1996) Behav Br Res. 74:45-55; Abi-Saab et al. (1998) Pharmacopsychiatry, 31:104-109). Further, it has also been shown that antipsychotic drugs that are effective in the treatment of schizophrenia reduce the locomotor activating effect of PCP (Gleason & Shannon (1997) Psychopharmacology, 129:79-84). These results demonstrate that locomotor activation induced by PCP is a useful model for screening of compounds which may be useful in the treatment of schizophrenia.

Amphetamine model of schizophrenia Amphetamine-induced increases in locomotor ambulation are well known and are widely used as a model of the positive symptoms of schizophrenia. This model is based on evidence that amphetamine increases motor behaviors and can induce a psychotic state in humans (Yui et al. (2000) Ann NY Acad Sci 914:1-12). Further, it is well known that amphetamine-induced increases in locomotor activity are blocked by antipsychotics drugs that are effective in the treatment of schizophrenia (Arnt (1995) Eur J Pharmacol 283:55-62). These results demonstrate that locomotor activation induced by amphetamine is a useful model for screening of compounds which may be useful in the treatment of schizophrenia.

Subjects: The present studies were performed in accordance with the animal care and use policies of Addex Pharmaceuticals and the EEC directives on the protection of animals used for experimental and other scientific purposes (86/609/EEC and subsequent revisions). Male C57BL6/j mice (20-30 g) 7 weeks of age at the time of delivery were group housed in a temperature and humidity controlled facility on a 12 hour light /dark cycle for at least 5 days before use. Mice had access to food and water ad libitum except during locomotor activity experiments.

Assessment of locomotor (ambulatory) activity: The effects of compounds on PCP- or amphetamine-induced locomotor activation in mice were tested. Locomotor activity

of mice was tested in white plastic boxes 35 cm X 35 cm square with walls 40 cm in height. Locomotor activity (ambulations) was monitored by a videotracking system (VideoTrack, Viewpoint, Champagne au Mont d'Or, France) that recorded the ambulatory movements of mice. Mice were naïve to the apparatus prior to testing. On test days, test compounds (200 mg/kg i.p. (intraperitoneal)) or vehicle were administered immediately before the PCP (5 mg/kg s.c.(sub-cutaneous), amphetamine (3.0 mg/kg s.c.) or saline injection. Mice were placed into the locomotor boxes immediately after the PCP, amphetamine or saline vehicle injection and their locomotor activity, defined as the distance traveled in centimeters (cm), was measured for 60 minutes.

Compound administration: Compounds were dissolved in dimethyl sulfoxide (DMSO) (4% of final volume) and then mixed with Labrafil M1944 CS (apricot kernel oil – Gattefossé, Saint Priest, France) (40% of final volume), sterile water (56% of final volume) and Tween 80 (10µL per 10 ml solution) and administered in a volume of 10 ml/kg. Compound-vehicle-treated mice received the equivalent volume of vehicle solution i.p. in the absence of added compound. PCP hydrochloride (Sigma, Switzerland) was dissolved in saline and was administered at a dose of 5 mg/kg s.c. in a volume of 10 ml/kg. PCP-vehicle-treated mice received an equal volume of saline vehicle injected s.c. D-amphetamine sulfate (Amino AG, Neuenhof, Switzerland) was dissolved in saline and administered at a dose of 3.0 mg/kg s.c. in a volume of 10 ml/kg. D-amphetamine-vehicle-treated mice received an equivalent volume of saline vehicle injected s.c.

Statistical analyses: Statistical analyses were performed using GraphPad PRISM statistical software (GraphPad, San Diego, CA, USA). Data were analyzed using unpaired t-tests. The significance level was set at $p<0.05$.

Effect of compounds on PCP-induced locomotor activity in mice

Data from such an experiment using a representative compound is shown below.

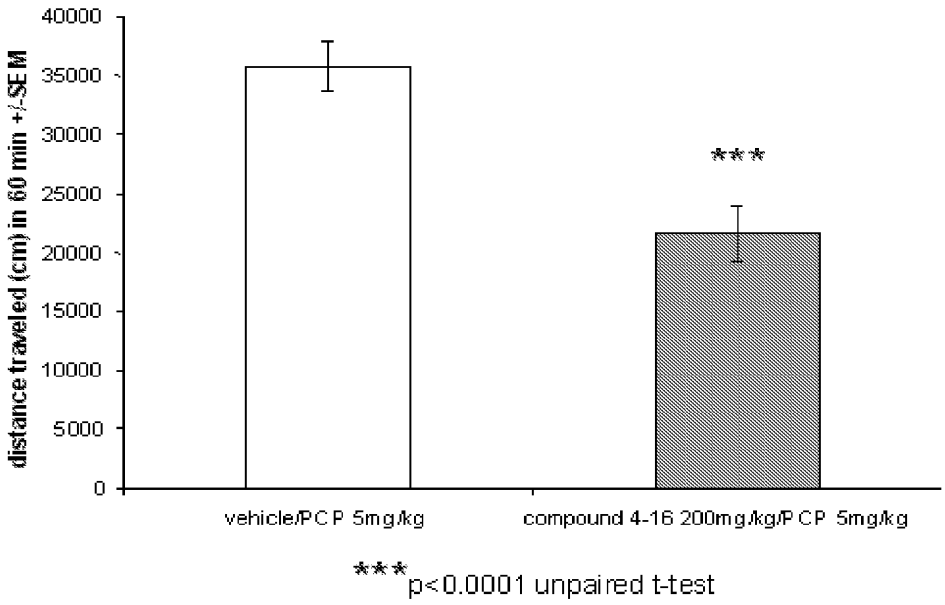


Figure D

As can be seen in the Figure D, the representative compound significantly attenuated the increase in locomotor activity induced by PCP (t=4.491, df=29, n=15 veh/PCP group; n=16 Compound 4-16/PCP group). These results suggest that compounds of Formula (I) may be useful in the treatment of schizophrenia.

Effect of compounds on amphetamine-induced locomotor activity in mice

Data from such an experiment using a representative compound is shown below.

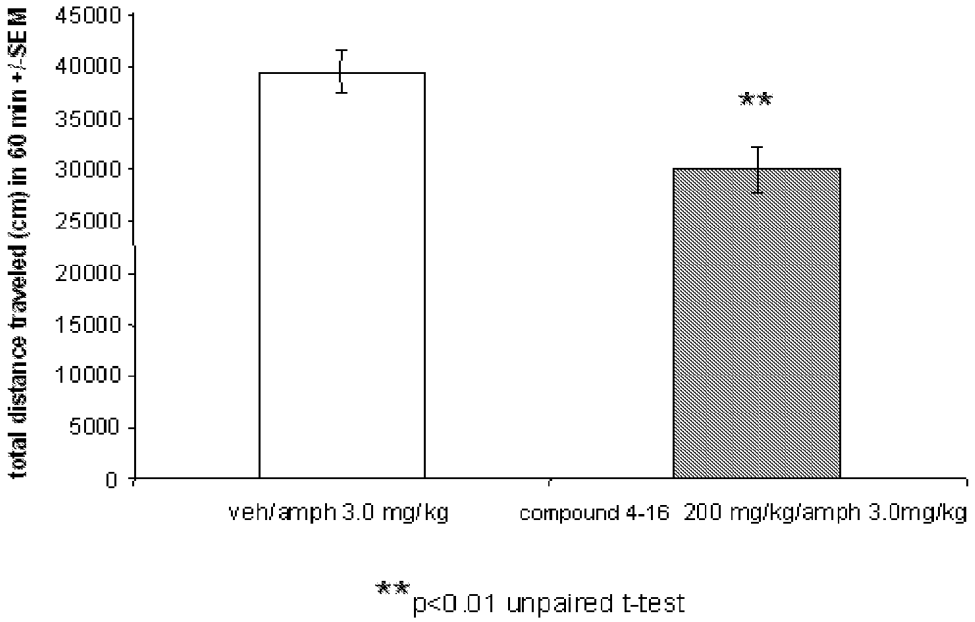


Figure E

As can be seen in the Figure E, the representative compound significantly attenuated the increase in locomotor activity induced by amphetamine (t=3.213, df=30, n=16 mice per group). These results suggest that compounds of Formula I may be useful in the treatment of schizophrenia.

Effect of compounds on baseline exploratory locomotor activity

The effect of Compound 4-16, a representative compound of the present invention, on exploratory (saline-treated) locomotor activity in mice is shown in below.

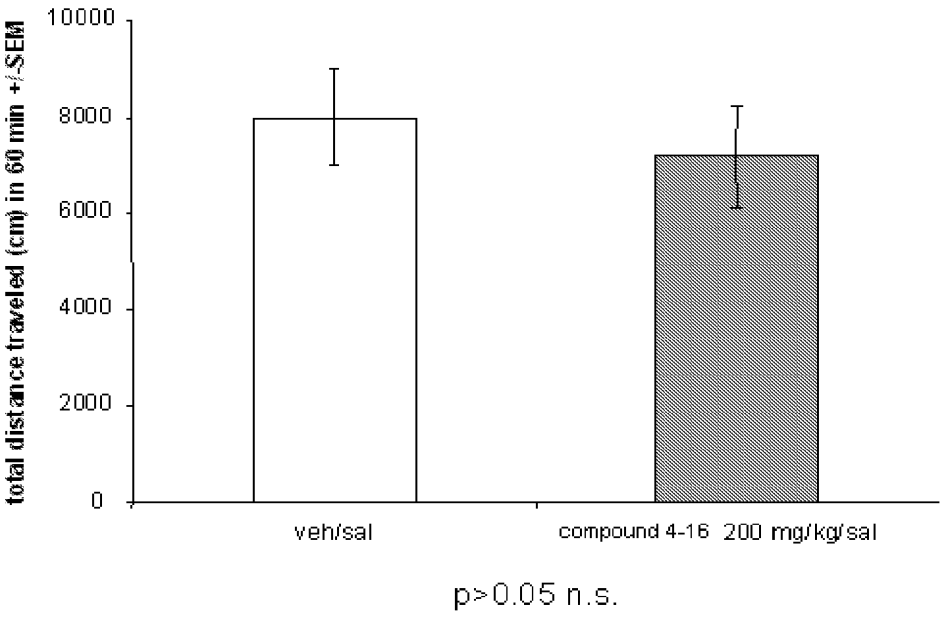


Figure F

As can be seen in the Figure F, Compound 4-16, had no statistically significant effect on locomotor activity in mice (t=0.5793, df=30, n=16 mice per group). These results demonstrate that Compound 4-16 has no effect on exploratory locomotor activity in non-habituated, saline-treated mice. Thus, attenuation by Compound 4-16, a representative compound of the present invention, of the hyperlocomotion induced by either PCP or amphetamine is specific to PCP- or amphetamine-induced hyperlocomotion and not a non-specific decrease in locomotor activity. These results further support the potential of compounds of Formula (I) in the treatment of schizophrenia.

FORMULATION EXAMPLES

Typical examples of recipes for the formulation of the invention are as follows:

1. Tablets

Compound 4-16	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg

Talcum	10 mg
Magnesium stearate	5 mg
Potato starch	ad 200 mg

In this Example, Compound 4-16 can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

2. Suspension

An aqueous suspension is prepared for oral administration so that each 1 milliliter contains 1 to 5 mg of one of the active compounds , 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

3. Injectable

A parenteral composition is prepared by stirring 1.5 % by weight of active ingredient of the invention in 10% by volume propylene glycol and water.

4. Ointment

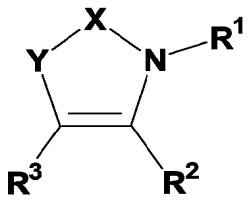
Compound 4-16	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

In this Example, Compound 4-16 can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

CLAIMS

1. Compound according to the general Formula (I),



(I)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

X is selected from C(=O), S(O), $S(O)_2$, $C(=NR^6)$ and C(=S);

Y is selected from S, $-C(R^4)=C(R^5)-$, $-C(R^5)=N-$, $-N=C(R^5)-$ and $-N(R^5)-$;

R^1 is not hydrogen and is an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkynyl, $-(C_2-C_6)$alkenyl, $-(C_3-C_7)$cycloalkyl, $-(C_3-C_8)$-cycloalkenyl, $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkylcyano and a radical $-V_1-T_1-M_1$;

T_1, V_1 are each independently a covalent bond or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl-, $-(C_2-C_6)$alkynyl-, $-(C_2-C_6)$alkenyl-, $-(C_3-C_7)$cycloalkyl-, $-(C_4-C_{10})$alkylcycloalkyl-, $-(C_3-C_8)$cycloalkenyl-, $-(C_1-C_6)$-alkylhalo-, $-(C_1-C_6)$alkylcyano-, $-(C_1-C_6)$alkyl-C(=O)-(C_0-C_6)alkyl-, $-(C_1-C_6)$-alkyl-C(=O)-(C_2-C_6)alkynyl-, $-(C_1-C_6)$alkyl-C(=O)-(C_2-C_6)alkenyl-, $-(C_1-C_6)$-alkyl-C(=O)-(C_3-C_7)cycloalkyl-, $-(C_1-C_6)$alkyl-C(=O)-(C_4-C_{10})alkylcycloalkyl-, $-(C_1-C_6)$alkyl-C(=O)O-(C_0-C_6)alkyl-, $-(C_1-C_6)$alkyl-C(=O)O-(C_2-C_6)alkynyl-, $-(C_1-C_6)$alkyl-C(=O)O-(C_2-C_6)alkenyl-, $-(C_1-C_6)$alkyl-C(=O)O-(C_3-C_7)-cycloalkyl-, $-(C_1-C_6)$alkyl-C(=O)O-(C_4-C_{10})alkylcycloalkyl-, $-(C_1-C_6)$alkyl-C(=O)NR^7-(C_0-C_6)alkyl-, $-(C_1-C_6)$alkyl-C(=O)NR^7-(C_2-C_6)alkynyl-, $-(C_1-C_6)$-alkyl-C(=O)NR^7-(C_2-C_6)alkenyl-, $-(C_1-C_6)$alkyl-C(=O)NR^7-(C_3-C_7)cycloalkyl-, $-(C_1-C_6)$alkyl-C(=O)NR^7-(C_4-C_{10})alkylcycloalkyl-, $-(C_1-C_6)$alkyl-O-(C_0-C_6)alkyl, $-(C_1-C_6)$alkyl-O-(C_2-C_6)alkynyl-, $-(C_1-C_6)$alkyl-O-(C_2-C_6)alkenyl-, $-(C_1-C_6)$alkyl-O-(C_3-C_7)cycloalkyl-, $-(C_1-C_6)$alkyl-O-(C_4-C_{10})alkylcycloalkyl-, $-(C_1-C_6)$alkyl-S-(C_0-C_6)alkyl-, $-(C_1-C_6)$alkyl-S-(C_2-C_6)alkynyl-, $-(C_1-C_6)$alkyl-S-(C_2-C_6)alkenyl-,

-(C_1-C_6)alkyl-S-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-S-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-S(O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-S(O)-(C_2-C_6)alkynyl-, -(C_1-C_6)-alkyl-S(O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-S(O)-(C_3-C_7)cycloalkyl-, -(C_1-C_6)-alkyl-S(O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-S(O)$_2$-(C_0-C_6)alkyl-, -(C_1-C_6)-alkyl-S(O)$_2$-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-S(O)$_2$-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-S(O)$_2$-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-S(O)$_2$-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)-alkyl-S(O)$_2$NR^7-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-S(O)$_2$NR^7-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-S(O)$_2$NR^7-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-S(O)$_2$NR^7-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-S(O)$_2$NR^7-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-NR^7-(C_0-C_6)-alkyl-, -(C_1-C_6)alkyl-NR^7-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^7-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^7-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^7-(C_4-C_{10})alkylcyclo-alkyl, -(C_1-C_6)alkyl-NR^{7}C(=O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)-(C_2-C_6)-alkynyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)-alkyl-NR^{7}C(=O)NR^8-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)NR^8-(C_2-C_6)-alkynyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)NR^8-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)NR^8-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)NR^8-(C_4-C_{10})-alkylcycloalkyl-, -(C_1-C_6)alkyl-NR^{7}S(O)$_2$-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^{7}S(O)$_2$-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^{7}S(O)$_2$-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^{7}S(O)$_2$-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^{7}S(O)$_2$-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=S)NR^8-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^{7}C(=S)NR^8-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^{7}C(=S)NR^8-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^{7}C(=S)NR^8-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=S)NR^8-(C_4-C_{10})-alkylcycloalkyl-, -(C_1-C_6)alkyl-OC(=O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-OC(=O)-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-OC(=O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-OC(=O)-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-OC(=O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_3-C_7)-cycloalkyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)O-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)O-(C_2-C_6)alkynyl-, -(C_1-C_6)-alkyl-NR^{7}C(=O)O-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)O-(C_3-C_7)-cycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)O-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-

$NR^7C(=NR^8)NR^9$-$(C_0$-$C_6)$alkyl-, -$(C_1$-$C_6)$alkyl-$NR^7C(=NR^8)NR^9$-$(C_2$-$C_6)$alkynyl-, -$(C_1$-$C_6)$alkyl-$NR^7C(=NR^8)NR^9$-$(C_2$-$C_6)$alkenyl-, -$(C_1$-$C_6)$alkyl-$NR^7C(=NR^8)NR^9$-$(C_3$-$C_7)$cycloalkyl-, -$(C_1$-$C_6)$alkyl-$NR^7C(=NR^8)NR^9$-$(C_4$-$C_{10})$alkylcycloalkyl-, -$(C_1$-$C_6)$alkyl-$NR^7C(=NR^8)$-$(C_0$-$C_6)$alkyl-, -$(C_1$-$C_6)$alkyl-$NR^7C(=NR^8)$-$(C_2$-$C_6)$-alkynyl-, -$(C_1$-$C_6)$alkyl-$NR^7C(=NR^8)$-$(C_2$-$C_6)$alkenyl-, -$(C_1$-$C_6)$alkyl-$NR^7C(=NR^8)$-$(C_3$-$C_7)$cycloalkyl-, -$(C_1$-$C_6)$alkyl-$NR^7C(=NR^8)$-$(C_4$-$C_{10})$alkylcycloalkyl-, -$(C_1$-$C_6)$alkyl-$C(=NR^7)NR^8$-$(C_0$-$C_6)$alkyl-, -$(C_1$-$C_6)$alkyl-$C(=NR^7)NR^8$-$(C_2$-$C_6)$alkynyl-, -$(C_1$-$C_6)$alkyl-$C(=NR^7)NR^8$-$(C_2$-$C_6)$alkenyl-, -$(C_1$-$C_6)$alkyl-$C(=NR^7)NR^8$-$(C_3$-$C_7)$cycloalkyl- and -$(C_1$-$C_6)$-alkyl$C(=NR^7)NR^8$-$(C_4$-$C_{10})$alkylcycloalkyl-;

R^2, R^3, R^4, R^5 and R^6 are each independently selected from the group of hydrogen, halogen, -CN, -OH, $-NO_2$, $-CF_3$, $-NH_2$, -SH, $-C(=NR^{10})NR^{11}R^{12}$, $-C(=O)R^{10}$, $-C(=NR^{10})R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, $-SR^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NR^{10}R^{11}$, $-NR^{10}C(=O)R^{11}$, $-NR^{10}C(=NR^{11})R^{12}$, $-NR^{10}C(=NR^{11})NR^{12}R^{13}$, $-NR^{10}C(=O)OR^{11}$, $-NR^{10}C(=O)NR^{11}R^{12}$, $-NR^{10}S(O)_2R^{11}$, $-S(O)_2NR^{10}R^{11}$, $-C(=S)NR^{10}R^{11}$, $-OC(=O)R^{10}$, $-OC(=O)NR^{10}R^{11}$, $-OR^{10}$, and an optionally substituted radical selected from the group of -$(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$-alkylhalo, -$(C_2$-$C_6)$alkynyl, -$(C_2$-$C_6)$alkenyl, -$(C_3$-$C_7)$cycloalkyl, -$(C_3$-$C_8)$-cycloalkenyl, -$(C_1$-$C_6)$alkylcyano, -$(C_1$-$C_6)$alkylaryl, -$(C_1$-$C_6)$alkylheteroaryl, aryl, heteroaryl and a radical $-V_2$-T_2-M_2;

T_2, V_2 are each independently a covalent bond or a radical selected from the group of -O-, -C(=O)-, -C(=O)O-, $-C(=O)NR^{10}$-, -S-, -S(O)-, $-S(O)_2$-, $-S(O)_2NR^{10}$-, $-NR^{10}$-, $-NR^{10}C(=O)$-, $-NR^{10}C(=O)NR^{11}$-, $-NR^{10}S(O)_2$-, $-NR^{10}C(=S)NR^{11}$-, -OC(=O)-, $-OC(=O)NR^{10}$, $-NR^{10}C(=O)O$-, and an optionally substituted radical selected from the group of -$(C_1$-$C_6)$alkyl-, -$(C_2$-$C_6)$alkynyl-, -$(C_2$-$C_6)$alkenyl-, -$(C_3$-$C_7)$cycloalkyl-, -$(C_3$-$C_8)$cycloalkenyl-, -$(C_1$-$C_6)$alkylhalo-, -$(C_1$-$C_6)$alkylcyano-, -$(C_0$-$C_6)$alkyl-O-$(C_1$-$C_6)$alkyl-, -$(C_0$-$C_6)$alkyl-O-$(C_2$-$C_6)$-alkynyl-, -$(C_0$-$C_6)$alkyl-O-$(C_2$-$C_6)$alkenyl-, -$(C_0$-$C_6)$alkyl-O-$(C_3$-$C_7)$cycloalkyl-, -$(C_0$-$C_6)$alkyl-O-$(C_4$-$C_{10})$alkylcycloalkyl-, -$(C_0$-$C_6)$alkyl-C(=O)-$(C_1$-$C_6)$alkyl-, -$(C_0$-$C_6)$alkyl-C(=O)-$(C_2$-$C_6)$alkynyl-, -$(C_0$-$C_6)$alkyl-C(=O)-$(C_2$-$C_6)$alkenyl-, -$(C_0$-$C_6)$alkyl-C(=O)-$(C_3$-$C_7)$alkylcycloalkyl-, -$(C_0$-$C_6)$alkyl-C(=O)-$(C_4$-$C_{10})$-cycloalkyl-, -$(C_0$-$C_6)$alkyl-C(=O)O-$(C_1$-$C_6)$alkyl-, -$(C_0$-$C_6)$alkyl-C(=O)O-$(C_2$-$C_6)$-

alkynyl-, -(C_0-C_6)alkyl-C(=O)O-(C_2-C_6)alkenyl-, -(C_0-C_6)alkyl-C(=O)O-(C_3-C_7)-cycloalkyl-, -(C_0-C_6)alkyl-C(=O)O-(C_4-C_{10})alkylcycloalkyl-, -(C_0-C_6)alkyl-C(=O)NR^{10}-(C_1-C_6)alkyl-, -(C_0-C_6)alkyl-C(=O)NR^{10}-(C_2-C_6)alkynyl-, -(C_0-C_6)-alkyl-C(=O)NR^{10}-(C_2-C_6)alkenyl-, -(C_0-C_6)alkyl-C(=O)NR^{10}-(C_3-C_7)cycloalkyl-, -(C_0-C_6)alkyl-C(=O)NR^{10}-(C_4-C_{10})alkylcycloalkyl-, -(C_0-C_6)alkyl-S-(C_1-C_6)alkyl-, -(C_0-C_6)alkyl-S-(C_2-C_6)alkynyl-, -(C_0-C_6)alkyl-S-(C_2-C_6)alkenyl-, -(C_0-C_6)alkyl-S-(C_3-C_7)cycloalkyl-, -(C_0-C_6)alkyl-S-(C_4-C_{10})alkylcycloalkyl-, -(C_0-C_6)alkyl-S(O)-(C_1-C_6)alkyl-, -(C_0-C_6)alkyl-O-(C_2-C_6)alkynyl-, -(C_0-C_6)alkyl-S(O)-(C_2-C_6)alkenyl-, -(C_0-C_6)alkyl-S(O)-(C_3-C_7)cycloalkyl-, -(C_0-C_6)alkyl-S(O)-(C_4-C_{10})alkylcycloalkyl-, -(C_0-C_6)alkyl-S(O)$_2$-(C_1-C_6)alkyl-, -(C_0-C_6)alkyl-S(O)$_2$-(C_2-C_6)alkynyl-, -(C_0-C_6)alkyl-S(O)$_2$-(C_2-C_6)alkenyl-, -(C_0-C_6)alkyl-S(O)$_2$-(C_3-C_7)cycloalkyl-, -(C_0-C_6)alkyl-S(O)$_2$-(C_4-C_{10})alkylcycloalkyl-, -(C_0-C_6)alkyl-S(O)$_2$$NR^{10}$-($C_1$-$C_6$)alkyl-, -($C_0$-$C_6$)alkyl-S(O)$_2$$NR^{10}$-($C_2$-$C_6$)alkynyl-, -($C_0$-$C_6$)alkyl-S(O)$_2$$NR^{10}$-($C_2$-$C_6$)alkenyl-, -($C_0$-$C_6$)alkyl-S(O)$_2$$NR^{10}$-($C_3$-$C_7$)cycloalkyl-, -($C_0$-$C_6$)alkyl-S(O)$_2$$NR^{10}$-($C_4$-$C_{10}$)alkylcycloalkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$-($C_1$-$C_6$)alkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$-($C_2$-$C_6$)alkynyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$-($C_2$-$C_6$)alkenyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$-($C_3$-$C_7$)cycloalkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$-($C_4$-$C_{10}$)-alkylcycloalkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=O)-($C_1$-$C_6$)alkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=O)-($C_2$-$C_6$)alkynyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=O)-($C_2$-$C_6$)alkenyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=O)-($C_3$-$C_7$)cycloalkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=O)-($C_4$-$C_{10}$)alkylcycloalkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=O)$NR^{11}$-($C_1$-$C_6$)alkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=O)$NR^{11}$-($C_2$-$C_6$)alkynyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=O)$NR^{11}$-($C_2$-$C_6$)alkenyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=O)$NR^{11}$-($C_3$-$C_7$)cycloalkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=O)$NR^{11}$-($C_4$-$C_{10}$)alkylcycloalkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$S(O)$_2$-($C_1$-$C_6$)-alkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$S(O)$_2$-($C_2$-$C_6$)alkynyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$S(O)$_2$-($C_2$-$C_6$)alkenyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$S(O)$_2$-($C_3$-$C_7$)cycloalkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$S(O)$_2$-($C_4$-$C_{10}$)alkylcycloalkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=S)$NR^{11}$-($C_1$-$C_6$)alkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=S)$NR^{11}$-($C_2$-$C_6$)alkynyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C-(=S)$NR^{11}$-($C_2$-$C_6$)alkenyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=S)$NR^{11}$-($C_3$-$C_7$)cycloalkyl-, -($C_0$-$C_6$)alkyl-$NR^{10}$C(=S)$NR^{11}$-($C_4$-$C_{10}$)alkylcycloalkyl-, -($C_0$-$C_6$)alkyl-OC(=O)-($C_1$-$C_6$)alkyl-, -($C_0$-$C_6$)alkyl-OC(=O)-($C_2$-$C_6$)alkynyl-, -($C_0$-$C_6$)alkyl-OC(=O)-($C_2$-$C_6$)alkenyl-, -($C_0$-$C_6$)alkyl-OC(=O)-($C_4$-$C_{10}$)alkylcycloalkyl-, -($C_0$-$C_6$)alkyl-

$OC(=O)$-$(C_3$-$C_7)$cycloalkyl-, -$(C_0$-$C_6)$alkyl-$OC(=O)NR^{10}$-$(C_1$-$C_6)$alkyl-, -$(C_0$-$C_6)$-alkyl-$OC(=O)NR^{10}$-$(C_2$-$C_6)$alkynyl-, -$(C_0$-$C_6)$alkyl-$OC(=O)NR^{10}$-$(C_2$-$C_6)$alkenyl-, -$(C_0$-$C_6)$alkyl-$OC(=O)NR^{10}$-$(C_4$-$C_{10})$alkylcycloalkyl-, -$(C_0$-$C_6)$alkyl-$OC(=O)NR^{10}$-$(C_3$-$C_7)$cycloalkyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=O)O$-$(C_1$-$C_6)$alkyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=O)O$-$(C_2$-$C_6)$alkynyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=O)O$-$(C_2$-$C_6)$alkenyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=O)O$-$(C_3$-$C_7)$cycloalkyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=O)O$-$(C_4$-$C_{10})$alkylcycloalkyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=NR^{11})NR^{12}$-$(C_1$-$C_6)$alkyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=NR^{11})NR^{12}$-$(C_2$-$C_6)$alkynyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=NR^{11})NR^{12}$-$(C_2$-$C_6)$alkenyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=NR^{11})NR^{12}$-$(C_3$-$C_7)$-cycloalkyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=NR^{11})NR^{12}$-$(C_4$-$C_{10})$alkylcycloalkyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=NR^{11})$-$(C_1$-$C_6)$alkyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=NR^{11})$-$(C_2$-$C_6)$-alkynyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=NR^{11})$-$(C_2$-$C_6)$alkenyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=NR^{11})$-$(C_3$-$C_7)$cycloalkyl-, -$(C_0$-$C_6)$alkyl-$NR^{10}C(=NR^{11})$-$(C_4$-$C_{10})$alkylcycloalkyl-, -$(C_0$-$C_6)$alkyl-$C(=NR^{10})NR^{11}$-$(C_1$-$C_6)$alkyl-, -$(C_0$-$C_6)$alkyl-$C(=NR^{10})NR^{11}$-$(C_2$-$C_6)$alkynyl-, -$(C_0$-$C_6)$alkyl-$C(=NR^{10})NR^{11}$-$(C_2$-$C_6)$alkenyl-, -$(C_0$-$C_6)$alkyl-$C(=NR^{10})NR^{11}$-$(C_3$-$C_7)$cycloalkyl- and -$(C_0$-$C_6)$alkyl-$C(=NR^{10})NR^{11}$-$(C_4$-$C_{10})$alkylcycloalkyl-;

(R^2 and R^3) or (R^4 and R^5) taken together may form an optionally substituted 3 to 10 membered ring selected from the group of aryl, heteroaryl, heterocyclic and cycloalkyl;

M_1 and M_2 are each independently selected from the group of hydrogen, -CN, -OH, $-NO_2$, $-CF_3$, $-NH_2$, -SH, $-C(=NR^{14})NR^{15}R^{16}$, $-C(=O)R^{14}$, $-C(=NR^{14})R^{15}$, $-C(=O)OR^{14}$, $-C(=O)NR^{14}R^{15}$, $-SR^{14}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-NR^{14}R^{15}$, $-NR^{14}C(=O)R^{15}$, $-NR^{14}C(=NR^{15})R^{16}$, $-NR^{14}C(=NR^{15})NR^{16}R^{17}$, $-NR^{14}C(=O)OR^{15}$, $-NR^{14}C(=O)NR^{15}R^{16}$, $-NR^{14}S(O)_2R^{15}$, $-C(=S)NR^{14}R^{15}$, $-OC(=O)R^{14}$, $-OC(=O)NR^{14}R^{15}$, $-OR^{14}$, $-S(O)_2NR^{14}R^{15}$, and an optionally substituted radical selected from the group of -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkynyl, -$(C_2$-$C_6)$alkenyl, -$(C_3$-$C_8)$cycloalkyl, -$(C_3$-$C_8)$cycloalkenyl and an optionally substituted 3 to 10 membered ring selected from the group of aryl, heteroaryl, heterocyclic and cycloalkyl ;

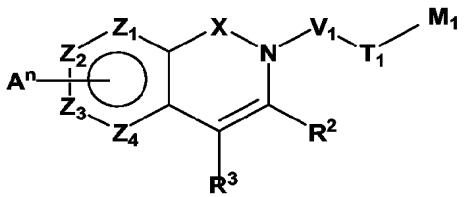
R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)-cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, -(C_1-C_6)alkylaryl, -(C_2-C_6)alkynyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkynyl-heteroaryl, -(C_2-C_6)alkynyl-aryl, -(C_2-C_6)alkenyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkenyl-heteroaryl and -(C_2-C_6)alkenyl-aryl;

R^7, R^8 and R^9 may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring or an optionally substituted 5 to 10 membered aromatic heterocyclic ring;

R^{10}, R^{11}, R^{12} and R^{13} may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring or an optionally substituted 5 to 10 membered aromatic heterocyclic ring; and

R^{14}, R^{15}, R^{16} and R^{17} may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring or an optionally substituted 5 to 10 membered aromatic heterocyclic ring.

2. Compound according to claim 1 having the Formula (II),



(II)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

X is selected from C(=O) and $S(O)_2$;

Z_1, Z_2, Z_3 and Z_4 are each independently, selected from the group of a covalent bond, C, S, N and O, representing a 5 or 6 membered heteroaryl or aryl ring which may further be substituted by 1 to 4 radicals A^n ;

A^n radicals are each independently selected from the group of hydrogen, halogen, -CN, -OH, $-NO_2$, $-CF_3$, -SH, $-NH_2$, and an optionally substituted radical selected

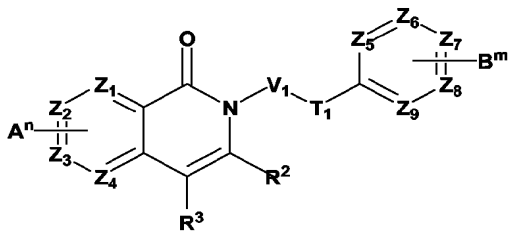
from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkynyl, -(C_2-C_6)-alkenyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)-alkylhalo, -O-(C_1-C_6)alkylcyano, -O-(C_3-C_6)alkynyl, -O-(C_3-C_7)cycloalkyl, -O-(C_2-C_6)alkenyl, -O-(C_2-C_6)alkyl-OR^{18}, -O-(C_1-C_6)alkyl-heteroaryl, -O-(C_0-C_6)-alkylaryl, -(C_0-C_6)alkyl-OR^{18}, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)-cycloalkyl-(C_1-C_6)alkyl, -O-heteroaryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, aryl, -O-aryl, -(C_1-C_6)alkylaryl, -(C_1-C_6)alkylhalo-OR^{18}, -(C_3-C_6)alkynyl-OR^{18}, -(C_3-C_6)alkenyl-OR^{18}, -(C_0-C_6)alkyl-S-R^{18}, -O-(C_2-C_6)alkyl-S-R^{18}, -(C_1-C_6)alkyl-S(=O)-R^{18}, -O-(C_1-C_6)alkyl-S(=O)-R^{18}, -(C_0-C_6)alkyl-S(=O)$_2$-R^{18}, -O-(C_1-C_6)-alkyl-S(=O)$_2$-R^{18}, -(C_0-C_6)alkyl-$NR^{18}R^{19}$, -O-(C_2-C_6)alkyl-$NR^{18}R^{19}$, -(C_0-C_6)-alkyl-S(=O)$_2$$NR^{18}R^{19}$, -($C_0$-$C_6$)alkyl-$NR^{18}$-S(=O)$_2$$R^{19}$, -O-($C_1$-$C_6$)alkyl-S(=O)$_2$$NR^{18}R^{19}$, -O-($C_1$-$C_6$)alkyl-$NR^{18}$-S(=O)$_2$$R^{19}$, -($C_0$-$C_6$)alkyl-C(=O)-$NR^{18}R^{19}$, -($C_0$-$C_6$)alkyl-$NR^{18}$C(=O)-$R^{19}$, -O-($C_1$-$C_6$)alkyl-C(=O)-$NR^{18}R^{19}$, -O-($C_1$-$C_6$)alkyl-$NR^{18}$C(=O)-$R^{19}$, -($C_0$-$C_6$)alkyl-OC(=O)-$R^{18}$, -($C_0$-$C_6$)alkyl-C(=O)-$OR^{18}$, -O-($C_1$-$C_6$)alkyl-OC(=O)-$R^{18}$, -O-($C_1$-$C_6$)alkyl-C(=O)-$OR^{18}$, -($C_0$-$C_6$)alkyl-C(=O)-$R^{18}$, -O-($C_1$-$C_6$)alkyl-C(=O)-$R^{18}$, -($C_0$-$C_6$)alkyl-$NR^{18}$-C(=O)-$OR^{19}$, -($C_0$-$C_6$)alkyl-O-C(=O)-$NR^{18}R^{19}$, -($C_0$-$C_6$)alkyl-$NR^{18}$-C(=$NR^{19}$)-$NR^{20}R^{21}$, -($C_0$-$C_6$)alkyl-$NR^{18}$-C(=O)-$NR^{19}R^{20}$, -($C_0$-$C_6$)alkyl-$NR^{18}$-C(=S)-$NR^{19}R^{20}$ and a -V_2-T_2-M_2 radical;

n is an integer ranging from 1 to 4;

R^{18}, R^{19}, R^{20} and R^{21} are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)-alkylcyano, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})-alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, -(C_1-C_6)alkylaryl, -(C_2-C_6)alkynyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkynyl-heteroaryl, -(C_2-C_6)alkynyl-aryl, -(C_2-C_6)alkenyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkenyl-heteroaryl and -(C_2-C_6)-alkenyl-aryl; and

R^{18}, R^{19}, R^{20} and R^{21} may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring or an optionally substituted 5 to 10 membered aromatic heterocyclic ring.

3. A compound according to claim 2 having Formula (II-a),



(II-a)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

Z_5, Z_6, Z_7, Z_8 and Z_9 are each independently selected from the group of a covalent bond, C, S, N and O, representing a 5 or 6 membered heteroaryl or aryl ring which may optionally be substituted by 1 to 5 radicals B^m ;

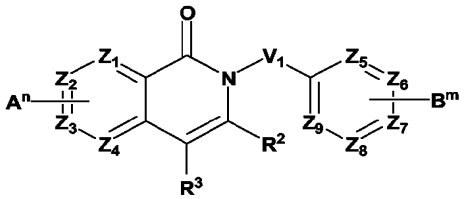
B^m radicals are each independently selected from the group of hydrogen, halogen, -CN, -OH, $-NO_2$, $-CF_3$, -SH, $-NH_2$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkynyl, -(C_2-C_6)-alkenyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)-alkylhalo, -O-(C_1-C_6)alkylcyano, -O-(C_3-C_6)alkynyl, -O-(C_3-C_7)cycloalkyl, -O-(C_2-C_6)alkenyl, -O-(C_2-C_6)alkyl-OR^{22}, -O-(C_1-C_6)alkyl-heteroaryl, -O-(C_0-C_6)-alkylaryl, -(C_0-C_6)alkyl-OR^{22}, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-heteroaryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, aryl, -O-aryl, -(C_1-C_6)alkylaryl, -(C_1-C_6)alkylhalo-OR^{22}, -(C_3-C_6)alkynyl-OR^{22}, -(C_3-C_6)alkenyl-OR^{22}, -(C_0-C_6)alkyl-S-R^{22}, -O-(C_2-C_6)alkyl-S-R^{22}, -(C_1-C_6)alkyl-S(=O)-R^{22}, -O-(C_1-C_6)alkyl-S(=O)-R^{22}, -(C_0-C_6)alkyl-$S(=O)_2$-R^{22}, -O-(C_1-C_6)-alkyl-$S(=O)_2$-R^{22}, -(C_0-C_6)alkyl-$NR^{22}R^{23}$, -O-(C_2-C_6)alkyl-$NR^{22}R^{23}$, -(C_0-C_6)alkyl-$S(=O)_2NR^{22}R^{23}$, -(C_0-C_6)alkyl-NR^{22}-$S(=O)_2R^{23}$, -O-(C_1-C_6)alkyl-$S(=O)_2NR^{22}R^{23}$, -O-(C_1-C_6)alkyl-NR^{22}-$S(=O)_2R^{23}$, -(C_0-C_6)alkyl-C(=O)-$NR^{22}R^{23}$, -(C_0-C_6)alkyl-NR^{22}C(=O)-R^{23}, -O-(C_1-C_6)alkyl-C(=O)-$NR^{22}R^{23}$, -O-(C_1-C_6)alkyl-NR^{22}C(=O)-R^{23}, -(C_0-C_6)alkyl-OC(=O)-R^{22}, -(C_0-C_6)alkyl-C(=O)-OR^{22}, -O-(C_1-C_6)alkyl-OC(=O)-R^{22}, -O-(C_1-C_6)alkyl-C(=O)-OR^{22}, -(C_0-C_6)alkyl-C(=O)-R^{22}, -O-(C_1-C_6)alkyl-C(=O)-R^{22}, -(C_0-C_6)alkyl-NR^{22}-C(=O)-OR^{23}, -(C_0-C_6)alkyl-O-C(=O)-$NR^{22}R^{23}$, -(C_0-C_6)alkyl-NR^{22}-C(=NR^{23})-$NR^{24}R^{25}$, -(C_0-C_6)alkyl-NR^{22}-C(=O)-$NR^{23}R^{24}$ and -(C_0-C_6)alkyl-NR^{22}-C(=S)-$NR^{23}R^{24}$;

m is an integer ranging from 1 to 5;

R^{22}, R^{23}, R^{24} and R^{25} are each independently selected from hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)-cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, -(C_1-C_6)alkylaryl, -(C_2-C_6)alkynyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkynyl-heteroaryl, -(C_2-C_6)alkynyl-aryl, -(C_2-C_6)alkenyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkenyl-heteroaryl and -(C_2-C_6)alkenyl-aryl; and

R^{22}, R^{23}, R^{24} and R^{25} may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring or an optionally substituted 5 to 10 membered aromatic heterocyclic ring.

4. A compound according to claim 3 having the Formula (II-b),



(II-b)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

V_1 is an optionally substituted radical selected from the group of -(C_1-C_6)alkyl-, -(C_2-C_6)alkynyl-, -(C_2-C_6)alkenyl-, -(C_3-C_7)cycloalkyl-, -(C_3-C_8)cycloalkenyl-, -(C_1-C_6)alkylhalo-, -(C_1-C_6)alkyl-C(=O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-C(=O)-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-C(=O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-C(=O)-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-C(=O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-C(=O)O-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-C(=O)O-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-C(=O)O-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-C(=O)O-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-C(=O)O-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-C(=O)NR^7-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-C(=O)NR^7-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-C(=O)NR^7-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-C(=O)NR^7-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-C(=O)NR^7-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-O-(C_0-C_6)alkyl-, -(C_1-C_6)-

alkyl-O-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-O-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-O-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-O-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-S-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-S-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-S-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-S-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-S-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-S(O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-S(O)-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-S(O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-S(O)-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-S(O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-S(O)$_2$-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-S(O)$_2$-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-S(O)$_2$-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-S(O)$_2$-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-S(O)$_2$-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-S(O)$_2$NR^7-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-S(O)$_2$NR^7-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-S(O)$_2$NR^7-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-S(O)$_2$NR^7-(C_3-C_7)cycloalkyl-, -(C_1-C_6)-alkyl-S(O)$_2$NR^7-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-NR^7-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^7-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^7-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^7-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^7-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)-alkyl-NR^{7}C(=O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)-(C_3-C_7)-cycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)NR^8-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)NR^8-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)NR^8-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)NR^8-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)NR^8-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)-alkyl-NR^{7}S(O)$_2$-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^{7}S(O)$_2$-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^{7}S(O)$_2$-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^{7}S(O)$_2$-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^{7}S(O)$_2$-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=S)NR^8-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^{7}C(=S)NR^8-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^{7}C(=S)NR^8-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^{7}C(=S)NR^8-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=S)NR^8-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-OC(=O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-OC(=O)-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-OC(=O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-OC(=O)-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-OC(=O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-NR^{7}C(=O)O-(C_0-C_6)alkyl-,

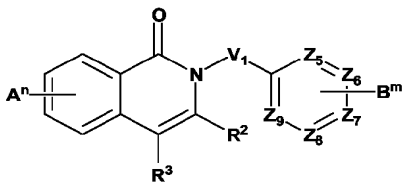
-(C_1-C_6)alkyl-$NR^7C(=O)O$-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-$NR^7C(=O)O$-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-$NR^7C(=O)O$-(C_3-C_7)cycloalkyl- and -(C_1-C_6)alkyl-$NR^7C(=O)O$-(C_4-C_{10})alkylcycloalkyl-;

R^2 is selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)alkylhalo, -O-(C_1-C_6)alkylcyano, -O-(C_3-C_6)alkynyl, -O-(C_3-C_7)cycloalkyl, -O-(C_2-C_6)alkyl-OR^{26}, -O-(C_1-C_6)alkyl-heteroaryl, -O-(C_0-C_6)-alkylaryl, -(C_0-C_6)alkyl-OR^{26}, -O-heteroaryl, -heteroaryl, -(C_1-C_6)alkyl-heteroaryl, -aryl, -O-aryl, -(C_1-C_6)alkylaryl, -(C_1-C_6)alkylhalo-OR^{26}, -(C_0-C_6)alkyl-SR^{26}, -(C_0-C_6)alkyl-$S(=O)_2$-R^{26}, -(C_0-C_6)alkyl-$NR^{26}R^{27}$, -O-(C_2-C_6)-alkyl-$NR^{26}R^{27}$, -(C_0-C_6)alkyl-$S(=O)_2NR^{26}R^{27}$, -(C_0-C_6)alkyl-NR^{26}-$S(=O)_2R^{27}$, -(C_0-C_6)alkyl-$C(=O)$-$NR^{26}R^{27}$, -(C_0-C_6)alkyl-$NR^{26}C(=O)$-R^{27}, -O-(C_1-C_6)-alkyl$C(=O)$-$NR^{26}R^{27}$, -O-(C_1-C_6)alkyl-$NR^{26}C(=O)$-R^{27} and -(C_0-C_6)alkyl-$C(=O)$-R^{26};

R^{26} and R^{27} are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkylcyano, -(C_0-C_6)alkyl, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, -(C_1-C_6)alkylaryl, -(C_2-C_6)alkynyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkynyl-heteroaryl, -(C_2-C_6)alkynyl-aryl, -(C_2-C_6)alkenyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkenyl-heteroaryl and -(C_2-C_6)alkenyl-aryl; and

R^{26} and R^{27} may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring or an optionally substituted 5 to 10 membered aromatic heterocyclic ring.

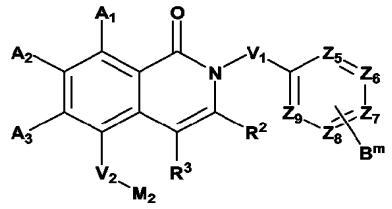
5. A compound according to claim 3 having the Formula (II-c),



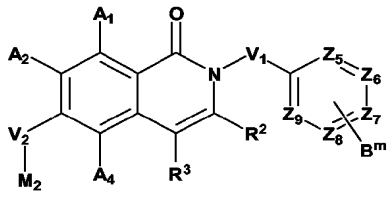
(II-c)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof.

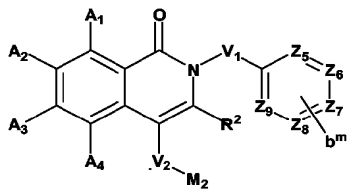
6. A compound according to claim 5 having one of the Formulas (II-c1), (II-c2) or (II-c3),



(II-c1)



(II-c2)



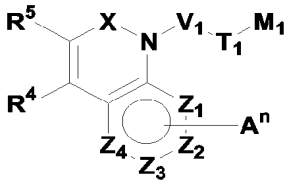
(II-c2)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

Z_5 ,Z_6 ,Z_7, Z_8 and Z_9 are selected from C or N, provided that at least 2 carbons are present and that a free position may further be substituted by 1 to 5 radicals B^m ; and

R^2, R^3, A^1, A^2, A^3 and A^4 are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, -OCF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_3-C_8)cycloalkenyl, -(C_1-C_6)alkylhalo, -(C_0-C_3)alkyl-O-(C_1-C_6)-alkyl, -(C_0-C_3)alkyl-O-(C_2-C_6)alkynyl, -(C_0-C_3)alkyl-O-(C_2-C_6)alkenyl, -(C_0-C_3)-alkyl-O-(C_3-C_7)cycloalkyl, -(C_0-C_3)alkyl-O-(C_4-C_{10})alkylcycloalkyl, -(C_0-C_3)-alkyl-O-(C_1-C_6)alkylhalo, -S-(C_1-C_6)alkyl, -S-(C_2-C_6)alkynyl, -S-(C_2-C_6)alkenyl, -S-(C_3-C_7)cycloalkyl, -S-(C_4-C_{10})alkylcycloalkyl, -(C_0-C_3)alkyl-$NR^{18}R^{19}$, -(C_0-C_3)alkyl-$S(O)_2NR^{18}R^{19}$, -(C_0-C_3)alkyl- $NR^{18}S(O)_2R^{19}$, -(C_0-C_3)alkyl-$C(=O)R^{18}$, -(C_0-C_3)alkyl-$C(=O)OR^{18}$, -(C_0-C_3)alkyl-$C(=O)NR^{18}R^{19}$, -(C_0-C_3)alkyl-$NR^{18}C(=O)R^{19}$, -O-(C_0-C_3)alkyl-$S(O)_2NR^{18}R^{19}$, -O-(C_0-C_3)alkyl-$NR^{18}S(O)_2R^{19}$, -O-(C_0-C_3)alkyl-$C(=O)R^{18}$, -O-(C_0-C_3)alkyl-$C(=O)OR^{18}$, -O-(C_0-C_3)alkyl-$C(=O)NR^{18}R^{19}$ and -O-(C_0-C_3)alkyl- $NR^{18}C(=O)R^{19}$.

7. A compound according to claim 1 having the Formula (III),



(III)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

X is selected from C(=O) and $S(O)_2$;

Z_1, Z_2, Z_3 and Z_4 are each independently, selected from the group of a covalent bond, C, S, N and O, representing a 5 or 6 membered heteroaryl or aryl ring which may further be substituted by 1 to 4 radicals A^n ;

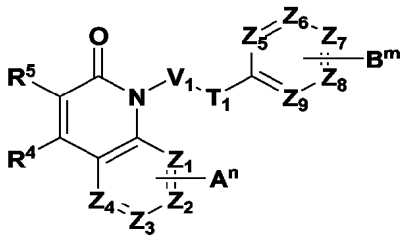
A^n radicals are each independently selected from the group of hydrogen, halogen, -CN, -OH, $-NO_2$, $-CF_3$, -SH, $-NH_2$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkynyl, -(C_2-C_6)-alkenyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)alkylhalo, -O-(C_1-C_6)alkylcyano, -O-(C_3-C_6)alkynyl, -O-(C_3-C_7)cycloalkyl, -O-(C_2-C_6)alkenyl, -O-(C_2-C_6)alkyl-OR^{18}, -O-(C_1-C_6)alkyl-heteroaryl, -O-(C_0-C_6)alkylaryl, -(C_0-C_6)alkyl-OR^{18}, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)-cycloalkyl-(C_1-C_6)alkyl, -O-heteroaryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, aryl, -O-aryl, -(C_1-C_6)alkylaryl, -(C_1-C_6)alkylhalo-OR^{18}, -(C_3-C_6)alkynyl-OR^{18}, -(C_3-C_6)alkenyl-OR^{18}, -(C_0-C_6)alkyl-SR^{18}, -O-(C_2-C_6)alkyl-SR^{18}, -(C_1-C_6)alkyl-$S(=O)R^{18}$, -O-(C_1-C_6)alkyl-$S(=O)R^{18}$, -(C_0-C_6)alkyl-$S(=O)_2R^{18}$, -O-(C_1-C_6)alkyl-$S(=O)_2R^{18}$, -(C_0-C_6)alkyl-$NR^{18}R^{19}$, -O-(C_2-C_6)alkyl-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-$S(=O)_2NR^{18}R^{19}$, -(C_0-C_6)alkyl-NR^{18}-$S(=O)_2R^{19}$, -O-(C_1-C_6)alkyl-$S(=O)_2NR^{18}R^{19}$, -O-(C_1-C_6)alkyl-NR^{18}-$S(=O)_2R^{19}$, -(C_0-C_6)alkyl-C(=O)-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-NR^{18}C(=O)-R^{19}, -O-(C_1-C_6)alkylC(=O)-$NR^{18}R^{19}$, -O-(C_1-C_6)alkyl-NR^{18}C(=O)-R^{19}, -(C_0-C_6)alkyl-OC(=O)-R^{19}, -(C_0-C_6)alkyl-C(=O)-OR^{18}, -O-(C_1-C_6)alkyl-OC(=O)-R^{18}, -O-(C_1-C_6)alkyl-C(=O)-OR^{18}, -(C_0-C_6)alkyl-C(=O)-R^{18}, -O-(C_1-C_6)-alkyl-C(=O)-R^{18}, -(C_0-C_6)alkyl-NR^{18}-C(=O)-OR^{19}, -(C_0-C_6)alkyl-O-C(=O)-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-NR^{18}-C(=NR^{19})-$NR^{20}R^{21}$, -(C_0-C_6)alkyl-NR^{18}-C(=O)-$NR^{19}R^{20}$, -(C_0-C_6)alkyl-NR^{18}-C(=S)-$NR^{19}R^{20}$, and a -V_2-T_2-M_2 radical;

n is an integer ranging from 1 to 4;

R^{18}, R^{19}, R^{20} and R^{21} are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)-alkylcyano, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})-alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, -(C_1-C_6)alkylaryl, -(C_2-C_6)alkynyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkynyl-heteroaryl, -(C_2-C_6)alkynyl-aryl, -(C_2-C_6)alkenyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkenyl-heteroaryl and -(C_2-C_6)-alkenyl-aryl; and

R^{18}, R^{19}, R^{20} and R^{21} may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring oran optionally substituted 5 to 10 membered aromatic heterocyclic ring.

8. A compound according to claim 7 having the Formula (III-a),



(III-a)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

Z_5, Z_6, Z_7, Z_8 and Z_9 are each independently selected from the group of a covalent bond, C, S, N and O, representing a 5 or 6 membered heteroaryl or aryl ring which may optionally be substituted by 1 to 5 radicals B^m ;

B^m radicals are each independently selected from the group of hydrogen, halogen, -CN, -OH, -NO_2, -CF_3, -SH, -NH_2, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkynyl, -(C_2-C_6)-alkenyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)-alkylhalo, -O-(C_1-C_6)alkylcyano, -O-(C_3-C_6)alkynyl, -O-(C_3-C_7)cycloalkyl, -O-(C_2-C_6)alkenyl, -O-(C_2-C_6)alkyl-OR^{22}, -O-(C_1-C_6)alkyl-heteroaryl, -O-(C_0-C_6)alkylaryl, -(C_0-C_6)alkyl-OR^{22}, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-heteroaryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl,

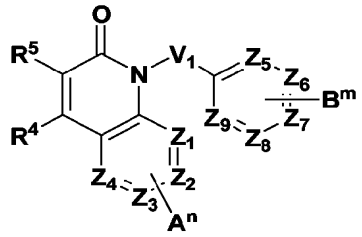
aryl, -O-aryl, -(C_1-C_6)alkylaryl, -(C_1-C_6)alkylhalo-OR^{22}, -(C_3-C_6)alkynyl-OR^{22}, -(C_3-C_6)alkenyl-OR^{22}, -(C_0-C_6)alkyl-S-R^{22}, -O-(C_2-C_6)alkyl-S-R^{22}, -(C_1-C_6)alkyl-S(=O)-R^{22}, -O-(C_1-C_6)alkyl-S(=O)-R^{22}, -(C_0-C_6)alkyl-S(=O)$_2$-R^{22}, -O-(C_1-C_6)-alkyl-S(=O)$_2$-R^{22}, -(C_0-C_6)alkyl-$NR^{22}R^{23}$, -O-(C_2-C_6)alkyl-$NR^{22}R^{23}$, -(C_0-C_6)-alkyl-S(=O)$_2$$NR^{22}R^{23}$, -($C_0$-$C_6$)alkyl-$NR^{22}$-S(=O)$_2$$R^{23}$, -O-($C_1$-$C_6$)alkyl-S(=O)$_2$$NR^{22}R^{23}$, -O-($C_1$-$C_6$)alkyl-$NR^{22}$-S(=O)$_2$$R^{23}$, -($C_0$-$C_6$)alkyl-C(=O)-$NR^{22}R^{23}$, -($C_0$-$C_6$)alkyl-$NR^{22}$C(=O)-$R^{23}$, -O-($C_1$-$C_6$)alkyl-C(=O)-$NR^{22}R^{23}$, -O-($C_1$-$C_6$)alkyl-$NR^{22}$C(=O)-$R^{23}$, -($C_0$-$C_6$)alkyl-OC(=O)-$R^{22}$, -($C_0$-$C_6$)alkyl-C(=O)-$OR^{22}$, -O-($C_1$-$C_6$)alkyl-OC(=O)-$R^{22}$, -O-($C_1$-$C_6$)alkyl-C(=O)-$OR^{22}$, -($C_0$-$C_6$)alkyl-C(=O)-$R^{22}$, -O-($C_1$-$C_6$)alkyl-C(=O)-$R^{22}$, -($C_0$-$C_6$)alkyl-$NR^{22}$-C(=O)-$OR^{23}$, -($C_0$-$C_6$)alkyl-O-C(=O)-$NR^{22}R^{23}$, -($C_0$-$C_6$)alkyl-$NR^{22}$-C(=$NR^{23}$)-$NR^{24}R^{25}$, -($C_0$-$C_6$)alkyl-$NR^{22}$-C(=O)-$NR^{23}R^{24}$ and -(C_0-C_6)alkyl-NR^{22}-C(=S)-$NR^{23}R^{24}$;

m is an integer from 1 to 5;

R^{22}, R^{23}, R^{24} and R^{25} are each independently selected from hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)-cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, -(C_1-C_6)alkylaryl, -(C_2-C_6)alkynyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkynyl-heteroaryl, -(C_2-C_6)alkynyl-aryl, -(C_2-C_6)alkenyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkenyl-heteroaryl or -(C_2-C_6)alkenyl-aryl; and

R^{22}, R^{23}, R^{24} and R^{25} may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring or an optionally substituted 5 to 10 membered aromatic heterocyclic ring.

9. A compound according to claim 8 having the Formula (III-b),



(III-b)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

V_1 is an optionally substituted radical selected from the group of -(C_1-C_6)alkyl-, -(C_2-C_6)alkynyl-, -(C_2-C_6)alkenyl-, -(C_3-C_7)cycloalkyl-, -(C_3-C_8)cycloalkenyl-, -(C_1-C_6)alkylhalo-, -(C_1-C_6)alkyl-C(=O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-C(=O)-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-C(=O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-C(=O)-(C_3-C_7)-cycloalkyl-, -(C_1-C_6)alkyl-C(=O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-C(=O)O-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-C(=O)O-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-C(=O)O-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-C(=O)O-(C_3-C_7)cycloalkyl-, -(C_1-C_6)-alkyl-C(=O)O-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-C(=O)NR^7-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-C(=O)NR^7-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-C(=O)NR^7-(C_2-C_6)-alkenyl-, -(C_1-C_6)alkyl-C(=O)NR^7-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-C(=O)NR^7-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-O-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-O-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-O-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-O-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-O-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-S-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-S-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-S-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-S-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-S-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-S(O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-S(O)-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-S(O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-S(O)-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-S(O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-$S(O)_2$-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-$S(O)_2$-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-$S(O)_2$-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-$S(O)_2$-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-$S(O)_2$-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-$S(O)_2NR^7$-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-$S(O)_2NR^7$-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-$S(O)_2NR^7$-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-$S(O)_2NR^7$-(C_3-C_7)cycloalkyl-, -(C_1-C_6)-alkyl-$S(O)_2NR^7$-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-NR^7-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^7-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^7-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^7-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^7-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)-alkyl-NR^7C(=O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^7C(=O)-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^7C(=O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^7C(=O)-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-NR^7C(=O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-NR^7C(=O)NR^8-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-NR^7C(=O)NR^8-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-NR^7C(=O)NR^8-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-NR^7C(=O)NR^8-(C_3-

C_7)cycloalkyl-, -(C_1-C_6)alkyl-$NR^7C(=O)NR^8$-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)-alkyl-$NR^7S(O)_2$-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-$NR^7S(O)_2$-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-$NR^7S(O)_2$-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-$NR^7S(O)_2$-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-$NR^7S(O)_2$-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-$NR^7C(=S)NR^8$-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-$NR^7C(=S)NR^8$-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-$NR^7C(=S)NR^8$-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-$NR^7C(=S)NR^8$-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-$NR^7C(=S)NR^8$-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-OC(=O)-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-OC(=O)-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-OC(=O)-(C_2-C_6)alkenyl-, -(C_1-C_6)alkyl-OC(=O)-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-OC(=O)-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_2-C_6)-alkenyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_3-C_7)cycloalkyl-, -(C_1-C_6)alkyl-OC(=O)NR^7-(C_4-C_{10})alkylcycloalkyl-, -(C_1-C_6)alkyl-$NR^7C(=O)O$-(C_0-C_6)alkyl-, -(C_1-C_6)alkyl-$NR^7C(=O)O$-(C_2-C_6)alkynyl-, -(C_1-C_6)alkyl-$NR^7C(=O)O$-(C_2-C_6)-alkenyl-, -(C_1-C_6)alkyl-$NR^7C(=O)O$-(C_3-C_7)cycloalkyl- and -(C_1-C_6)alkyl-$NR^7C(=O)O$-(C_4-C_{10})alkylcycloalkyl- ;

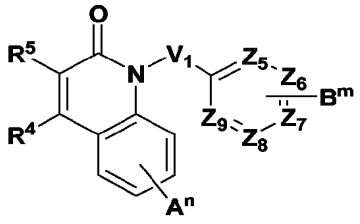
R^2 is selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)alkylhalo, -O-(C_1-C_6)alkylcyano, -O-(C_3-C_6)alkynyl, -O-(C_3-C_7)cycloalkyl, -O-(C_2-C_6)alkyl-OR^{26}, -O-(C_1-C_6)alkyl-heteroaryl, -O-(C_0-C_6)-alkylaryl, -(C_0-C_6)alkyl-OR^{26}, -O-heteroaryl, -heteroaryl, -(C_1-C_6)alkyl-heteroaryl, -aryl, -O-aryl, -(C_1-C_6)alkylaryl, -(C_1-C_6)alkylhalo-OR^{26}, -(C_0-C_6)-alkyl-SR^{26}, -(C_0-C_6)alkyl-$S(=O)_2$-R^{26}, -(C_0-C_6)alkyl-$NR^{26}R^{27}$, -O-(C_2-C_6)alkyl-$NR^{26}R^{27}$, -(C_0-C_6)alkyl-$S(=O)_2NR^{26}R^{27}$, -(C_0-C_6)alkyl-NR^{26}-$S(=O)_2R^{27}$, -(C_0-C_6)alkyl-C(=O)-$NR^{26}R^{27}$, -(C_0-C_6)alkyl-$NR^{26}C(=O)$-R^{27}, -O-(C_1-C_6)alkylC(=O)-$NR^{26}R^{27}$, -O-(C_1-C_6)alkyl-$NR^{26}C(=O)$-R^{27} and -(C_0-C_6)alkyl-C(=O)-R^{26};

R^{26} and R^{27} are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkylcyano, -(C_0-C_6)alkyl, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, -(C_1-C_6)alkylaryl, -(C_2-C_6)alkynyl-(C_3-

C_7)cycloalkyl, -(C_2-C_6)alkynyl-heteroaryl, -(C_2-C_6)alkynyl-aryl, -(C_2-C_6)alkenyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkenyl-heteroaryl and -(C_2-C_6)alkenyl-aryl; and

R^{26} and R^{27} may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring or an optionally substituted 5 to 10 membered aromatic heterocyclic ring.

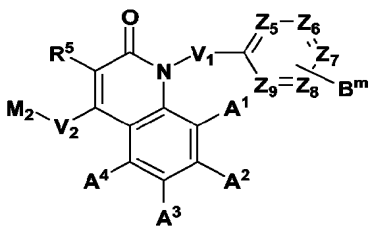
10. A compound according to claim 9 having the Formula (III-c),



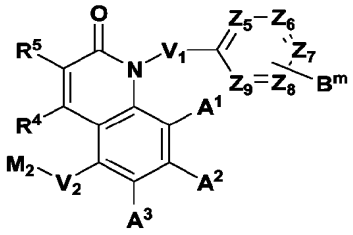
(III-c)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof.

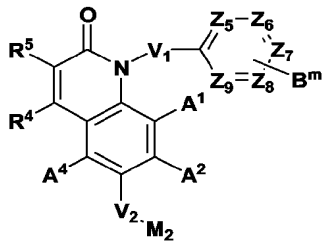
11. A compound according to claim 10 having one of the Formulas (III-c1), (III-c2) or (III-c3),



(III-c1)



(III-c2)



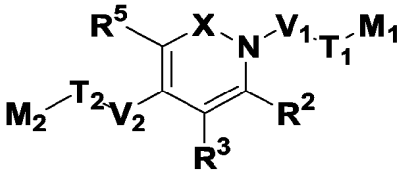
(III-c2)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

Z_5, Z_6, Z_7, Z_8 and Z_9 are selected from C or N, provided that at least 2 carbons are present and that a free position may further be substituted by 1 to 5 radicals B^m ; and

R^4, R^5, A^1, A^2, A^3 and A^4 are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, -OCF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_3-C_8)cycloalkenyl, -(C_1-C_6)alkylhalo, -(C_0-C_3)alkyl-O-(C_1-C_6)-alkyl, -(C_0-C_3)alkyl-O-(C_2-C_6)alkynyl, -(C_0-C_3)alkyl-O-(C_2-C_6)alkenyl, -(C_0-C_3)-alkyl-O-(C_3-C_7)cycloalkyl, -(C_0-C_3)alkyl-O-(C_4-C_{10})alkylcycloalkyl, -(C_0-C_3)-alkyl-O-(C_1-C_6)alkylhalo, -S-(C_1-C_6)alkyl, -S-(C_2-C_6)alkynyl, -S-(C_2-C_6)alkenyl, -S-(C_3-C_7)cycloalkyl, -S-(C_4-C_{10})alkylcycloalkyl, -(C_0-C_3)alkyl-$NR^{18}R^{19}$, -(C_0-C_3)alkyl-$S(O)_2NR^{18}R^{19}$, -(C_0-C_3)alkyl- $NR^{18}S(O)_2R^{19}$, -(C_0-C_3)alkyl-$C(=O)R^{18}$, -(C_0-C_3)alkyl-$C(=O)OR^{18}$, -(C_0-C_3)alkyl-$C(=O)NR^{18}R^{19}$, -(C_0-C_3)alkyl-$NR^{18}C(=O)R^{19}$, -O-(C_0-C_3)alkyl-$S(O)_2NR^{18}R^{19}$, -O-(C_0-C_3)alkyl-$NR^{18}S(O)_2R^{19}$, -O-(C_0-C_3)alkyl-$C(=O)R^{18}$, -O-(C_0-C_3)alkyl-$C(=O)OR^{18}$, -O-(C_0-C_3)alkyl-$C(=O)NR^{18}R^{19}$ and -O-(C_0-C_3)alkyl-$NR^{18}C(=O)R^{19}$.

12. A compound according to claim 1 having the Formula (IV),



(IV)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

X is selected from C(=O) and $S(O)_2$;

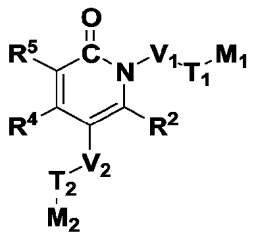
R^2, R^3 and R^5 are each independently selected from the group of hydrogen, halogen, -CN, -OH, -NO_2, -CF_3, -SH, -NH_2, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)alkylhalo, -O-(C_1-C_6)alkylcyano, -O-(C_3-C_6)alkynyl, -O-(C_3-C_7)cycloalkyl, -O-(C_2-C_6)alkenyl, -O-(C_2-C_6)alkyl-OR^{18}, -O-(C_1-C_6)alkyl-heteroaryl, -O-(C_0-C_6)-alkylaryl, -(C_0-C_6)alkyl-OR^{18}, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)-cycloalkyl-(C_1-C_6)alkyl, -O-heteroaryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, aryl, -O-aryl, -(C_1-C_6)alkylaryl, -(C_1-C_6)alkylhalo-OR^{18}, -(C_3-C_6)alkynyl-OR^{18}, -(C_3-

C_6)alkenyl-OR^{18}, -(C_0-C_6)alkyl-SR^{18}, -O-(C_2-C_6)alkyl-SR^{18}, -(C_1-C_6)alkyl-$S(=O)R^{18}$, -O-(C_1-C_6)alkyl-$S(=O)R^{18}$, -(C_0-C_6)alkyl-$S(=O)_2R^{18}$, -O-(C_1-C_6)alkyl-$S(=O)_2R^{18}$, -(C_0-C_6)alkyl-$NR^{18}R^{19}$, -(C_0-C_3)alkyl-O-(C_2-C_6)alkyl-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-$S(=O)_2NR^{18}R^{19}$, -(C_0-C_6)alkyl-NR^{18}-$S(=O)_2R^{19}$, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl-$S(=O)_2NR^{18}R^{19}$, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl-NR^{18}-$S(=O)_2R^{19}$, -(C_0-C_6)alkyl-$C(=O)$-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-$NR^{18}C(=O)$-R^{19}, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl$C(=O)$-$NR^{18}R^{19}$, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl-$NR^{18}C(=O)$-R^{19}, -(C_0-C_6)-alkyl-$OC(=O)$-R^{18}, -(C_0-C_6)alkyl-$C(=O)$-OR^{18}, -O-(C_1-C_6)alkyl-$OC(=O)$-R^{18}, -O-(C_1-C_6)alkyl-$C(=O)$-OR^{18}, -(C_0-C_6)alkyl-$C(=O)$-R^{18}, -O-(C_1-C_6)alkyl-$C(=O)$-R^{18}, -(C_0-C_6)alkyl-NR^{18}-$C(=O)$-OR^{19}, -(C_0-C_6)alkyl-O-$C(=O)$-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-NR^{18}-$C(=NR^{19})$-$NR^{20}R^{21}$, -(C_0-C_6)alkyl-NR^{18}-$C(=O)$-$NR^{19}R^{20}$ and -(C_0-C_6)alkyl-NR^{18}-$C(=S)$-$NR^{19}R^{20}$;

R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from hydrogen and an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, -(C_1-C_6)alkylaryl, -(C_2-C_6)alkynyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkynyl-heteroaryl, -(C_2-C_6)alkynyl-aryl, -(C_2-C_6)alkenyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkenyl-heteroaryl and -(C_2-C_6)alkenyl-aryl; and

R^{18}, R^{19}, R^{20} and R^{21} may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring or an optionally substituted 5 to 10 membered aromatic heterocyclic ring.

13. A compound according to claim 1 having the Formula (V),



(V)

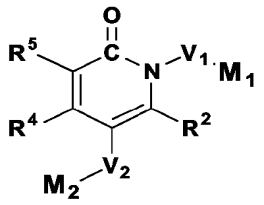
a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

R^2, R^4 and R^5 are each independently selected from the group of hydrogen, halogen, -CN, -OH, $-NO_2$, $-CF_3$, -SH, $-NH_2$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)alkylhalo, -O-(C_1-C_6)alkylcyano, -O-(C_3-C_6)alkynyl, -O-(C_3-C_7)cycloalkyl, -O-(C_2-C_6)alkenyl, -O-(C_2-C_6)alkyl-OR^{18}, -O-(C_1-C_6)alkyl-heteroaryl, -O-(C_0-C_6)alkylaryl, -(C_0-C_6)alkyl-OR^{18}, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-heteroaryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, aryl, -O-aryl, -(C_1-C_6)alkylaryl, -(C_1-C_6)alkylhalo-OR^{18}, -(C_3-C_6)alkynyl-OR^{18}, -(C_3-C_6)alkenyl-OR^{18}, -(C_0-C_6)alkyl-SR^{18}, -O-(C_2-C_6)alkyl-SR^{18}, -(C_1-C_6)alkyl-$S(=O)R^{18}$, -O-(C_1-C_6)alkyl-$S(=O)R^{18}$, -(C_0-C_6)alkyl-$S(=O)_2R^{18}$, -O-(C_1-C_6)alkyl-$S(=O)_2R^{18}$, -(C_0-C_6)alkyl-$NR^{18}R^{19}$, -(C_0-C_3)alkyl-O-(C_2-C_6)alkyl-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-$S(=O)_2NR^{18}R^{19}$, -(C_0-C_6)alkyl-NR^{18}-$S(=O)_2R^{19}$, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl-$S(=O)_2NR^{18}R^{19}$, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl-NR^{18}-$S(=O)_2R^{19}$, -(C_0-C_6)alkyl-$C(=O)$-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-$NR^{18}C(=O)$-R^{19}, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl$C(=O)$-$NR^{18}R^{19}$, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl-$NR^{18}C(=O)$-R^{19}, -(C_0-C_6)-alkyl-$OC(=O)$-R^{18}, -(C_0-C_6)alkyl-$C(=O)$-OR^{18}, -O-(C_1-C_6)alkyl-$OC(=O)$-R^{18}, -O-(C_1-C_6)alkyl-$C(=O)$-OR^{18}, -(C_0-C_6)alkyl-$C(=O)$-R^{18}, -O-(C_1-C_6)alkyl-$C(=O)$-R^{18}, -(C_0-C_6)alkyl-NR^{18}-$C(=O)$-OR^{19}, -(C_0-C_6)alkyl-O-$C(=O)$-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-NR^{18}-$C(=NR^{19})$-$NR^{20}R^{21}$, -(C_0-C_6)alkyl-NR^{18}-$C(=O)$-$NR^{19}R^{20}$ and -(C_0-C_6)alkyl-NR^{18}-$C(=S)$-$NR^{19}R^{20}$;

R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from hydrogen and an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)-cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, -(C_1-C_6)alkylaryl, -(C_2-C_6)alkynyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkynyl-heteroaryl, -(C_2-C_6)alkynyl-aryl, -(C_2-C_6)alkenyl-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkenyl-heteroaryl and -(C_2-C_6)alkenyl-aryl; and

R^{18}, R^{19}, R^{20} and R^{21} may be taken together to form an optionally substituted 3 to 10 membered non-aromatic heterocyclic ring or an optionally substituted 5 to 10 membered aromatic heterocyclic ring.

14. A compound according to claim 13 having the Formula (V-a),



(V-a)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

V_1 is not a covalent bond ;

V_2 is selected from the group of a covalent bond, -O-, -C(=O)-, -C(=O)O-, -C(=O)NR^{10}-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2NR^{10}$-, -NR^{10}-, -$NR^{10}C(=O)$-, -$NR^{10}C(=O)NR^{11}$-, -$NR^{10}S(O)_2$-, -$NR^{10}C(=S)NR^{11}$-, -OC(=O)-, -OC(=O)NR^{10}, -$NR^{10}C(=O)O$-, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_3-C_8)-cycloalkenyl, -(C_1-C_6)alkylhalo, -O-(C_1-C_6)alkyl, -O-(C_2-C_6)alkynyl, -O-(C_2-C_6)-alkenyl, -O-(C_3-C_7)cycloalkyl, -O-(C_4-C_{10})alkylcycloalkyl, -C(=O)-(C_1-C_6)alkyl, -C(=O)-(C_2-C_6)alkynyl, -C(=O)-(C_2-C_6)alkenyl, -C(=O)-(C_3-C_7)alkylcycloalkyl, -C(=O)-(C_4-C_{10})cycloalkyl, -C(=O)O-(C_1-C_6)alkyl, -C(=O)O-(C_2-C_6)alkynyl, -C(=O)O-(C_2-C_6)alkenyl, -C(=O)O-(C_3-C_7)cycloalkyl, -C(=O)O-(C_4-C_{10})alkylcycloalkyl, -C(=O)NR^{10}-(C_1-C_6)alkyl, -C(=O)NR^{10}-(C_2-C_6)alkynyl, -C(=O)NR^{10}-(C_2-C_6)alkenyl, -C(=O)NR^{10}-(C_3-C_7)cycloalkyl, -C(=O)NR^{10}-(C_4-C_{10})alkylcycloalkyl, -S-(C_1-C_6)alkyl, -S-(C_2-C_6)alkynyl, -S-(C_2-C_6)alkenyl, -S-(C_3-C_7)cycloalkyl, -S-(C_4-C_{10})alkylcycloalkyl, -S(O)-(C_1-C_6)alkyl, -O-(C_2-C_6)alkynyl, -S(O)-(C_2-C_6)alkenyl, -S(O)-(C_3-C_7)cycloalkyl, -S(O)-(C_4-C_{10})alkylcycloalkyl, -$S(O)_2$-(C_1-C_6)alkyl, -$S(O)_2$-(C_2-C_6)alkynyl, -$S(O)_2$-(C_2-C_6)alkenyl, -$S(O)_2$-(C_3-C_7)cycloalkyl, -$S(O)_2$-(C_4-C_{10})alkylcycloalkyl, -$S(O)_2NR^{10}$-(C_1-C_6)alkyl, -$S(O)_2NR^{10}$-(C_2-C_6)alkynyl, -$S(O)_2NR^{10}$-(C_2-C_6)-alkenyl, -$S(O)_2NR^{10}$-(C_3-C_7)cycloalkyl, -$S(O)_2NR^{10}$-(C_4-C_{10})alkylcycloalkyl, -NR^{10}-(C_1-C_6)alkyl, -NR^{10}-(C_2-C_6)alkynyl, -NR^{10}-(C_2-C_6)alkenyl, -NR^{10}-(C_3-C_7)cycloalkyl, -NR^{10}-(C_4-C_{10})alkylcycloalkyl, -$NR^{10}C(=O)$-(C_1-C_6)alkyl, -$NR^{10}C(=O)$-(C_2-C_6)alkynyl, -$NR^{10}C(=O)$-(C_2-C_6)alkenyl, -$NR^{10}C(=O)$-(C_3-

C_7)cycloalkyl, -NR^{10}C(=O)-(C_4-C_{10})alkylcycloalkyl, -NR^{10}C(=O)NR^{11}-(C_1-C_6)alkyl, -NR^{10}C(=O)NR^{11}-(C_2-C_6)alkynyl, -NR^{10}C(=O)NR^{11}-(C_2-C_6)alkenyl, -NR^{10}C(=O)NR^{11}-(C_3-C_7)cycloalkyl, -NR^{10}C(=O)NR^{11}-(C_4-C_{10})alkylcycloalkyl, -NR^{10}S(O)$_2$-(C_1-C_6)alkyl, -NR^{10}S(O)$_2$-(C_2-C_6)alkynyl, -NR^{10}S(O)$_2$-(C_2-C_6)alkenyl, -NR^{10}S(O)$_2$-(C_3-C_7)cycloalkyl, -NR^{10}S(O)$_2$-(C_4-C_{10})alkylcycloalkyl, -NR^{10}C(=S)NR^{11}-(C_1-C_6)alkyl, -NR^{10}C(=S)NR^{11}-(C_2-C_6)alkynyl, -NR^{10}C(=S)-NR^{11}-(C_2-C_6)alkenyl, -NR^{10}C(=S)NR^{11}-(C_3-C_7)cycloalkyl, -NR^{10}C(=S)NR^{11}-(C_4-C_{10})alkylcycloalkyl, -OC(=O)-(C_1-C_6)alkyl, -OC(=O)-(C_2-C_6)alkynyl, -OC(=O)-(C_2-C_6)alkenyl, -OC(=O)-(C_4-C_{10})alkylcycloalkyl, -OC(=O)-(C_3-C_7)cycloalkyl, -OC(=O)NR^{10}-(C_1-C_6)alkyl, -OC(=O)NR^{10}-(C_2-C_6)alkynyl, -OC(=O)NR^{10}-(C_2-C_6)alkenyl, -OC(=O)NR^{10}-(C_4-C_{10})alkylcycloalkyl, -OC(=O)NR^{10}-(C_3-C_7)cycloalkyl, -NR^{10}C(=O)O-(C_1-C_6)alkyl, -NR^{10}C(=O)O-(C_2-C_6)alkynyl, -NR^{10}C(=O)O-(C_2-C_6)alkenyl, -NR^{10}C(=O)O-(C_3-C_7)cycloalkyl, -NR^{10}C(=O)O-(C_4-C_{10})alkylcycloalkyl, -NR^{10}C(=NR^{11})NR^{12}-(C_1-C_6)alkyl, -NR^{10}C(=NR^{11})-NR^{12}-(C_2-C_6)alkynyl, -NR^{10}C(=NR^{11})NR^{12}-(C_2-C_6)alkenyl, -NR^{10}C(=NR^{11})NR^{12}-(C_3-C_7)cycloalkyl, -NR^{10}C(=NR^{11})NR^{12}-(C_4-C_{10})alkylcycloalkyl, -NR^{10}C(=NR^{11})-(C_1-C_6)alkyl, -NR^{10}C(=NR^{11})-(C_2-C_6)alkynyl, -NR^{10}C(=NR^{11})-(C_2-C_6)alkenyl, -NR^{10}C(=NR^{11})-(C_3-C_7)cycloalkyl, -NR^{10}C(=NR^{11})-(C_4-C_{10})alkylcycloalkyl, -C(=NR^{10})NR^{11}-(C_1-C_6)alkyl, -C(=NR^{10})NR^{11}-(C_2-C_6)alkynyl, -C(=NR^{10})NR^{11}-(C_2-C_6)alkenyl, -C(=NR^{10})NR^{11}-(C_3-C_7)cycloalkyl and -C(=NR^{10})NR^{11}-(C_4-C_{10})alkylcycloalkyl; and

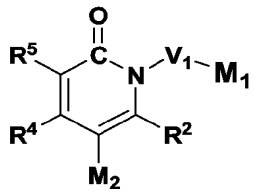
R^2, R^4 and R^5 are each independently selected from the group of hydrogen, halogen, -CN, -OH, -NO_2, -CF_3, -SH, -NH_2, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)alkylhalo, -O-(C_1-C_6)alkylcyano, -O-(C_3-C_6)alkynyl, -O-(C_3-C_7)cycloalkyl, -O-(C_2-C_6)alkenyl, -O-(C_2-C_6)alkyl-OR^{18}, -O-(C_1-C_6)alkyl-heteroaryl, -O-(C_0-C_6)-alkylaryl, -(C_0-C_6)alkyl-OR^{18}, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)-cycloalkyl-(C_1-C_6)alkyl, -O-heteroaryl, -(C_1-C_6)alkyl-heteroaryl, -O-aryl, -(C_1-C_6)alkylaryl, -(C_1-C_6)alkylhalo-OR^{18}, -(C_3-C_6)alkynyl-OR^{18}, -(C_3-C_6)alkenyl-OR^{18}, -(C_0-C_6)alkyl-SR^{18}, -O-(C_2-C_6)alkyl-SR^{18}, -(C_1-C_6)alkyl-S(=O)R^{18}, -O-(C_1-C_6)alkyl-S(=O)R^{18}, -(C_0-C_6)alkyl-S(=O)$_2R^{18}$, -O-(C_1-C_6)alkyl-S(=O)$_2R^{18}$, -(C_0-

C_6)alkyl-$NR^{18}R^{19}$, -(C_0-C_3)alkyl-O-(C_2-C_6)alkyl-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-$S(=O)_2NR^{18}R^{19}$, -(C_0-C_6)alkyl-NR^{18}-$S(=O)_2R^{19}$, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl-$S(=O)_2NR^{18}R^{19}$, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl-NR^{18}-$S(=O)_2R^{19}$, -(C_0-C_6)alkyl-$C(=O)$-$NR^{18}R^{19}$, -(C_0-C_6)alkyl-$NR^{18}C(=O)$-R^{19}, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl$C(=O)$-$NR^{18}R^{19}$, -(C_0-C_3)alkyl-O-(C_1-C_6)alkyl-$NR^{18}C(=O)$-R^{19}, -(C_0-C_6)alkyl-$OC(=O)$-R^{18}, -(C_0-C_6)alkyl-$C(=O)$-OR^{18}, -O-(C_1-C_6)alkyl-$OC(=O)$-R^{18}, -O-(C_1-C_6)alkyl-$C(=O)$-OR^{18}, -(C_0-C_6)alkyl-$C(=O)$-R^{18} and -O-(C_1-C_6)alkyl-$C(=O)$-R^{18}.

15. A compound according to claim 14 wherein :

V_2 is selected from the group of a covalent bond, -O-, -C(=O)-, -C(=O)O-, -$C(=O)NR^{10}$-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2NR^{10}$-, -NR^{10}-, -$NR^{10}C(=O)$-, -$NR^{10}C(=O)NR^{11}$-, -$NR^{10}S(O)_2$-, -$NR^{10}C(=S)NR^{11}$-, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_2-C_6)alkynyl, -(C_2-C_6)-alkenyl, -(C_3-C_7)cycloalkyl, -(C_3-C_8)cycloalkenyl, -(C_1-C_6)alkylhalo, -O-(C_1-C_6)-alkyl, -O-(C_3-C_7)cycloalkyl, -C(=O)-(C_1-C_6)alkyl, -C(=O)-(C_4-C_{10})cycloalkyl, -C(=O)O-(C_1-C_6)alkyl, -C(=O)O-(C_3-C_7)cycloalkyl, -$C(=O)NR^{10}$-(C_1-C_6)alkyl, -$C(=O)NR^{10}$-(C_3-C_7)cycloalkyl, -S-(C_1-C_6)alkyl, -S-(C_3-C_7)cycloalkyl, -S(O)-(C_1-C_6)alkyl, -S(O)-(C_3-C_7)cycloalkyl, -$S(O)_2$-(C_1-C_6)alkyl, -$S(O)_2$-(C_3-C_7)cycloalkyl, -$S(O)_2NR^{10}$-(C_1-C_6)alkyl, -$S(O)_2NR^{10}$-(C_3-C_7)cycloalkyl, -NR^{10}-(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -$NR^{10}C(=O)$-(C_1-C_6)alkyl, -$NR^{10}C(=O)$-(C_3-C_7)cycloalkyl, -$NR^{10}C(=O)NR^{11}$-(C_1-C_6)alkyl, -$NR^{10}C(=O)NR^{11}$-(C_3-C_7)cycloalkyl, -$NR^{10}S(O)_2$-(C_1-C_6)alkyl and -$NR^{10}S(O)_2$-(C_3-C_7)cycloalkyl.

16. A compound according to claim 15 having the Formula (V-b),



(V-b)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

V_1 is an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylhalo, -(C_1-C_6)-alkyl-C(=O)-(C_0-C_6)alkyl, -(C_1-C_6)alkyl-C(=O)NR^7-(C_0-C_6)alkyl, -(C_1-C_6)alkyl-O-(C_0-C_6)alkyl, -(C_0-C_6)alkyl-S(O)$_2$-(C_0-C_6)alkyl, -(C_1-C_6)alkyl-S(O)$_2NR^7$-(C_0-C_6)alkyl, -(C_1-C_6)alkyl-NR^7-(C_0-C_6)alkyl, -(C_1-C_6)alkyl-NR^7C(=O)-(C_0-C_6)alkyl and -(C_1-C_6)alkyl-NR^7S(O)$_2$-(C_0-C_6)alkyl;

R^7 is a radical selected from the group of hydrogen, -(C_1-C_6)alkyl, -(C_1-C_6)-alkylhalo, -(C_2-C_6)alkynyl, -(C_2-C_6)alkenyl, -(C_3-C_7)cycloalkyl or -(C_1-C_6)-alkylcyano; and

M_1 and M_2 are each independently hydrogen or an optionally substituted radical selected from the group of aryl, heteroaryl and (C_3-C_7)cycloalkyl.

17. A compound according to claim 16 wherein :

V_1 is -(C_1-C_6)alkyl, optionally substituted by one or more -OCH_3, -OCF_3, -CF_3, fluoro or cyano radicals ; and

M_1 and M_2 are each independently an optionally substituted radical selected from hydrogen, aryl, thienyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, benzoimidazolyl, benzooxazolyl, benzothiazolyl, thionaphtyl, indolyl, pyrimidinyl, quinolyl, cyclohexyl and cyclopentyl.

18. Compound according to any of claims 1 to 17, a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein :

X is C(=O);

Y is selected from -C(R^4)=C(R^5)-, -C(R^5)=N- and -N=C(R^5)- ;

R^1 is an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo and a radical -V_1-T_1-M_1;

T_1, V_1 are each independently a covalent bond or an optionally substituted radical, preferably substituted with hydroxy, halo and halo(C_1-C_6)alkyl, selected from the group of -(C_1-C_6)alkyl- ; -(C_2-C_6)alkenyl-, -(C_2-C_6)alkynyl- ; -(C_1-C_6)-

alkyl-C(=O)-(C_0-C_6)alkyl- ; -(C_1-C_6)alkyl-C(=O)NR^7-(C_0-C_6)alkyl- wherein R^7 is hydrogen or -(C_1-C_6)alkyl- ; and -(C_1-C_6)alkyl-O-(C_0-C_6)alkyl- ;

R^2, R^3, R^4 and R^5 are each independently selected from the group of hydrogen, halogen, -CN, $-NO_2$, $-C(=O)OR^{10}$, $-OR^{10}$, and an optionally substituted radical, preferably substituted with hydroxy, selected from the group of -(C_1-C_6)alkyl and a radical -V_2-T_2-M_2 ;

T_2, V_2 are each independently a covalent bond or a radical selected from the group of -O- ; -C(=O)- ; $-NR^{10}$- and an optionally substituted radical, preferably substituted with hydroxy, selected from the group of -(C_1-C_6)alkyl- ; -(C_2-C_6)-alkenyl- ; -(C_2-C_6)alkynyl- ; -(C_0-C_6)alkyl-O-(C_1-C_6)alkyl- ; and -(C_0-C_6)alkyl-NR^{10}-(C_1-C_6)alkyl- wherein R^{10} is preferably hydrogen or (C_1-C_6)alkyl;

(R^2 and R^3) or (R^4 and R^5) taken together may form an aryl optionally substituted with n radicals A^n equal to -V_2-M_2 ;

M_1 and M_2 are each independently selected from the group of hydrogen, an optionally substituted -(C_1-C_6)alkyl-radical and an optionally substituted 3 to 10 membered ring selected from the group of (C_{1-6})cycloalkyl ; aryl, preferably phenyl or naphthyl ; heteroaryl and heterocyclic, preferably pyridinyl, indolyl, , imidazolyl, oxadiazolyl, isoxazolyl, furyl, thienyl, thiazolyl, benzothiazolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, quinoxalinyl, benzoxazolyl, benzodioxolyl, benzotetrahydrofuryl and benzothienyl ; wherein the optional substitution on any of the aforementioned rings is selected from the group of (C_1-C_6)alkyl; (C_1-C_6)alkyloxy; hydroxy(C_1-C_6)alkyloxy;(C_1-C_6)alkyloxy(C_1-C_6)alkyl; (C_1-C_6)alkyloxy(C_1-C_6)alkyloxy; (C_1-C_6)alkyloxycarbonyl; (C_1-C_6)-alkyloxycarbonyl(C_1-C_6)alkyl; (C_1-C_6)alkyloxycarbonyloxy; (C_1-C_6)-alkyloxycarbonyl(C_1-C_6)alkyloxy; (C_1-C_6)alkylcarbonyl; (C_1-C_6)-alkylcarbonyl(C_1-C_6)alkyloxy; (C_1-C_6)alkylcarbonyloxy; (C_1-C_6)alkylthieno;

(C_1-C_6)alkylsulfonyl ; heterocyclic-sulfonyl, preferably morpholinylsulfonyl and pyrrolidinylsulfonyl; (C_1-C_6)alkylsulfonylamino; (C_1-C_6)alkenyl; aryl, preferably phenyl; carboxyl(C_1-C_6)alkyl; carbonyl(C_1-C_6)alkyloxy; halo, preferably fluoro and chloro; hydroxy; hydroxy(C_1-C_6)alkyl; phenyl(C_1-C_6)alkyloxy; cyano;cyano(C_1-C_6)alkyloxy; trifluoro(C_1-C_6)alkyl; trifluoro(C_1-C_6)alkyloxy;

amino; amino(C_1-C_6)alkyloxy; mono- and di((C_1-C_6)alkyl)amino; mono- and di((C_1-C_6)alkylcarbonyl)amino; mono- and di((C_1-C_6)alkyloxycarbonyl)amino; mono- and di((C_1-C_6)alkylcarbonyl)amino(C_1-C_6)alkyl; mono- and di((C_1-C_6)-alkylsulfonyl)amino(C_1-C_6)alkyloxy; mono- and di((C_1-C_6)alkyl)amino(C_1-C_6)-alkyloxy; mono- and di((C_1-C_6)alkylcarbonyl)amino(C_1-C_6)alkyloxy; mono- and di((C_1-C_6)alkyl)aminocarbonyl; mono- and di((C_1-C_6)alkyl)aminocarbonyl(C_1-C_6)alkyl; mono- and di((C_1-C_6)alkyl)aminocarbonyl(C_1-C_6)alkyloxo; mono- and di((C_1-C_6)alkyl)amino(C_1-C_6)alkylamino; nitro; tri(C_1-C_6)alkylsilyl; heterocyclic, preferably morpholinyl; heterocyclic-(C_1-C_6)alkyl, preferably (C_1-C_6)-alkyltetrazolyl; and heterocyclic-(C_1-C_6)alkyloxy, the heterocyclic preferably being pyridinyl, morpholinyl, pyrrolidinyl, optionally substituted with oxo, isoxazolyl, imidazolyl, tetrazolyl or thiazolyl ;

R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} are each independently hydrogen or an optionally substituted -(C_1-C_6)alkyl-radical ;

A^n is hydrogen or halo ; and

n is an integer equal to 0 or 1.

19. A compound according to any one of claims 1 to 18, wherein said compound is selected from the List of Particular Preferred Compounds, listed in the description and a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an N-oxide form thereof.

20. A compound according to any one of claims 1 to 19, which exist as optical isomers, wherein said compound is either the racemic mixture or the individual optical isomer.

21. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 19 and a pharmaceutically acceptable carrier and/or excipient.

22. A compound according to any one of claims 1 to 19 for use as a medicament.

23. Use of a compound according to any one of claims 1 to 19 or a pharmaceutical composition according to claim 21 for the manufacture of a medicament for treating or preventing a condition in a mammal, including a human, the treatment

or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 positive allosteric modulators.

24. Use of a compound according to any one of claims 1 to 19 or a pharmaceutical composition according to claim 21 for the manufacture of a medicament for treating, or preventing, ameliorating, controlling or reducing the risk of various neurological and psychiatric disorders associated with glutamate dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 positive allosteric modulators.

25. Use according to any one of claims 23 and 24, wherein the condition or disorder is a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

26. Use according to claim 25, wherein the central nervous system disorder is an anxiety disorder, selected from the group of agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), social phobia and other phobias.

27. Use according to claim 25, wherein the central nervous system disorder is a psychotic disorder selected from the group of schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder and substance-induced psychotic disorder.

28. Use according to claim 25, wherein the central nervous system disorder is a personality disorder selected from the group of obsessive-compulsive personality disorder and schizoid, schizotypal disorder.

29. Use according to claim 25, wherein the central nervous system disorder is a substance-related disorder selected from the group of alcohol abuse, alcohol dependence, alcohol withdrawal, alcohol withdrawal delirium, alcohol-induced psychotic disorder, amphetamine dependence, amphetamine withdrawal, cocaine dependence, cocaine withdrawal, nicotine dependence, nicotine withdrawal, opioid dependence and opioid withdrawal.

30. Use according to claim 25, wherein the central nervous system disorder is an eating disorder selected from the group of anorexia nervosa and bulimia nervosa.

31. Use according to claim 25, wherein the central nervous system disorder is a mood disorder selected from the group of bipolar disorders (I & II), cyclothymic disorder, depression, dysthymic disorder, major depressive disorder and substance-induced mood disorder.

32. Use according to claim 25, wherein the central nervous system disorder is migraine.

33. Use according to claim 25, wherein the central nervous system disorder is epilepsy or a convulsive disorder selected from the group of generalized nonconvulsive epilepsy, generalized convulsive epilepsy, petit mal status epilepticus, grand mal status epilepticus, partial epilepsy with or without impairment of consciousness, infantile spasms, epilepsy partialis continua, and other forms of epilepsy.

34. Use according to claim 25, wherein the childhood disorder is attention-deficit/hyperactivity disorder.

35. Use according to claim 25, wherein the central nervous system disorder is a cognitive disorder selected from the group of delirium, substance-induced persisting delirium, dementia, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, dementia of the Alzheimer's type, substance-induced persisting dementia and mild cognitive impairment.

36. Use according to claim 25, wherein the central nervous system disorder is selected from the group of anxiety, schizophrenia, migraine, depression, and epilepsy.

37. Use according to any one of claims 25 to 36, wherein the mGluR2 positive allosteric modulator has an ED_{50} of about 1 μM or less.

38. Use of a compound according to claims 1 to 19 for the preparation of a tracer for imaging a metabotropic glutamate receptor.

39. Use of a compound according to any one of claims 1 to 19 in combination with an orthosteric agonist of mGluR2 for the manufacture of a medicament for treating or preventing a condition as cited in any one of claims 23 to 37, in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 allosteric modulators.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/054636

A. CLASSIFICATION OF SUBJECT MATTER
C07D213/64 C07D401/10 C07D407/10 C07D413/10 C07D409/10
A61K31/4412 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2006	31/01/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Menegaki, F

INTERNATIONAL SEARCH REPORT

Information on patent family members

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